NOTES FOR PATHOPHYSIOLOGY

B.Pharmacy 2nd SEM

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UNIT - I

Definitions

Patient: Individual affected by a disease or any abnormality

Lesions: Characteristic alterations occurring within cells and tissues as a result of disease

Etiology: Factors causing a disease

Idiopathic Disease: The diseases for which the cause remains unknown

Iatrogenic Disease: The disease arising as a direct consequence of medical treatment provided

Pathogenesis: Study of the progression of a disease

Acute Disease: A short term illness that develops very quickly with marked signs

Chronic Disease: A milder condition developing gradually, but persists and causes more permanent tissue damage

Syndrome: Collection of signs and symptoms that usually occur together in response to a condition

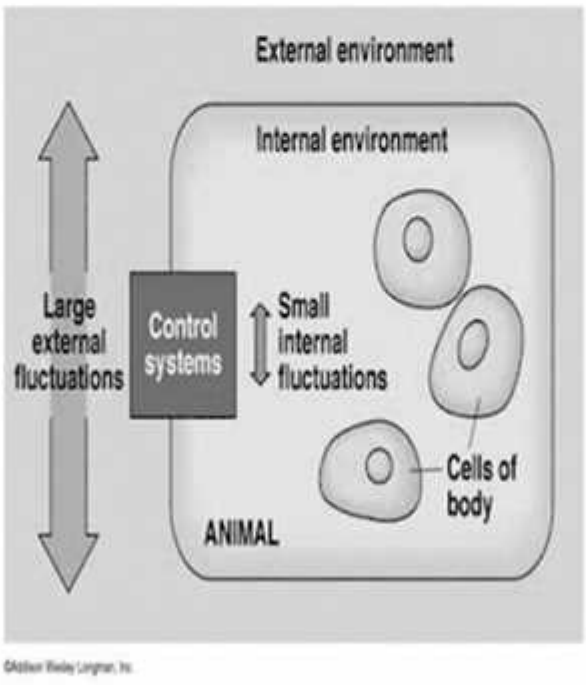
Prognosis: The probability for recovery or other outcomes.

Homeostasis

Homeostasis is any self-regulating process by which an organism tends to maintain stability while adjusting to conditions that are best for its survival

HOMEOSTATIC CONTROL MECHANISMS

- Homeostatic control mechanisms work through 'Feedback Mechanisms'.
- Status of a body condition is continually monitored, evaluated, changed, re-monitored & reevaluated.



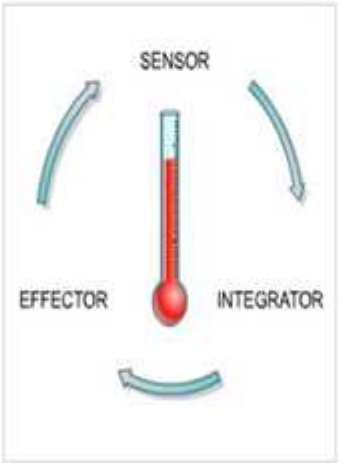
FEEDBACK MECHANISM

- A feedback mechanism is a cycle in which the output of a system "feeds back" to either modify or reinforce the action taken by the system.

- A feedback mechanism may operate at:
  - Tissue level
  - Organ level
  - Organ system level
  - Body level, integrating with other organ systems.
  - Feedback mechanism can be:
  - **Negative feedback (more common)**
  - **Positive feedback**

A FEEDBACK SYSTEM CONSISTS OF THREE COMPONENTS

1. **SENSOR (RECEPTOR):** detects specific changes (stimuli) in the environment.
2. **INTEGRATOR:** act to direct impulses to the place where a response can be made.
3. **EFFECTOR:** performs the appropriate response.



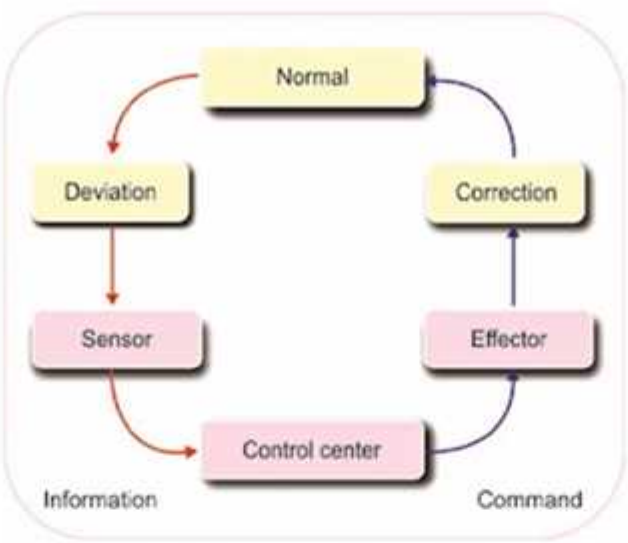
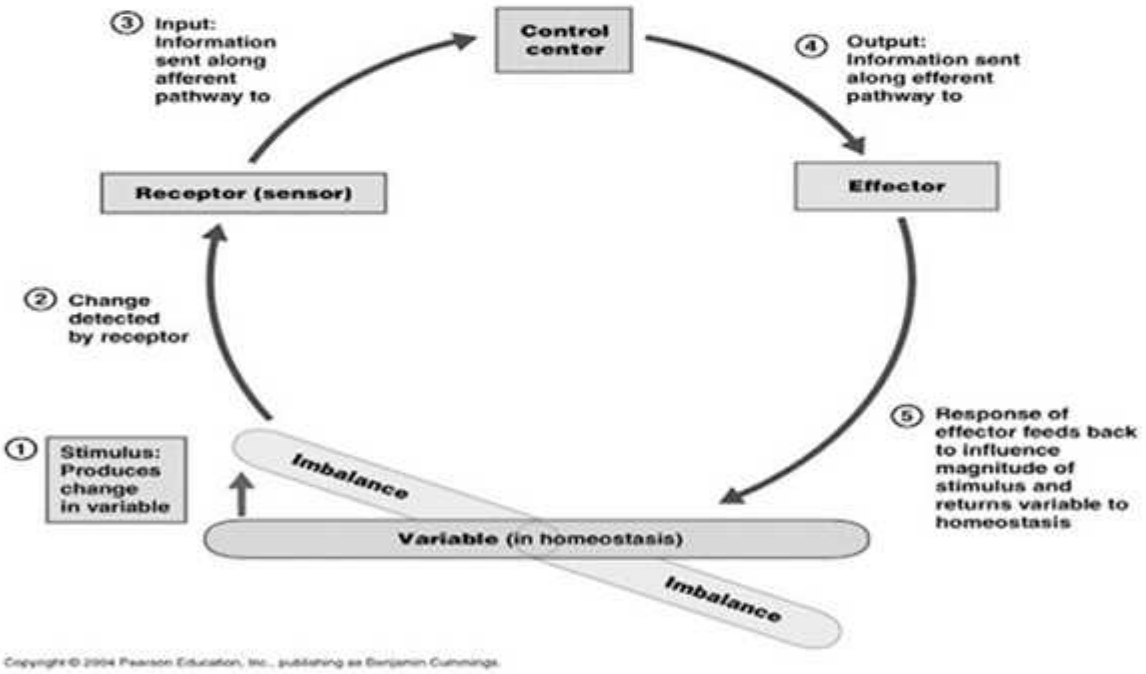


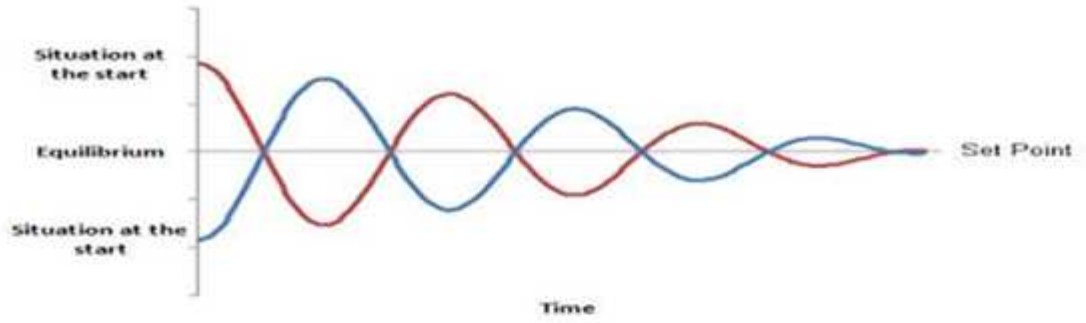
FIGURE 4.1: Components of homeostatic system

A FEEDBACK LOOP

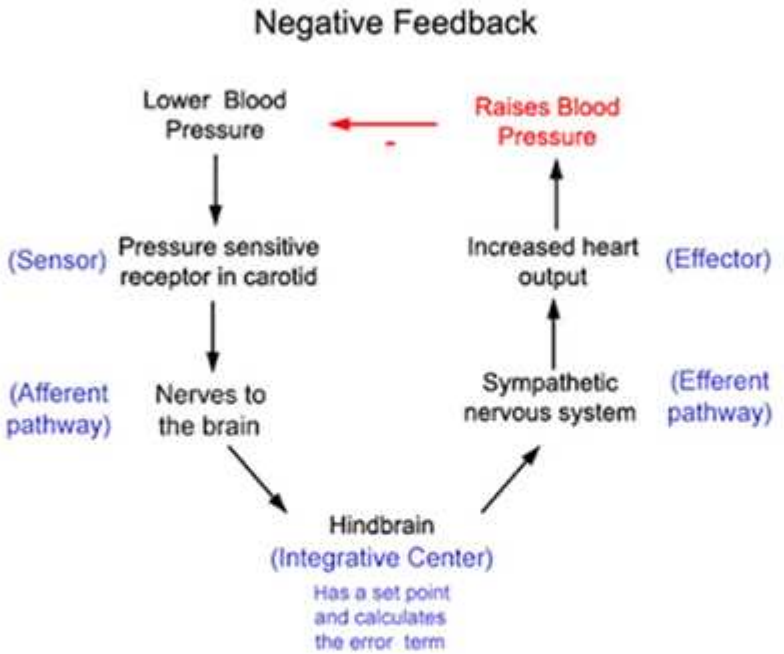


NEGATIVE FEEDBACK

- Mechanisms that maintain the factor at some mean value.
- Reverse a change
- Restore abnormal values to normal



EXAMPLE: NEGATIVE FEEDBACK BLOOD PRESSURE REGULATION



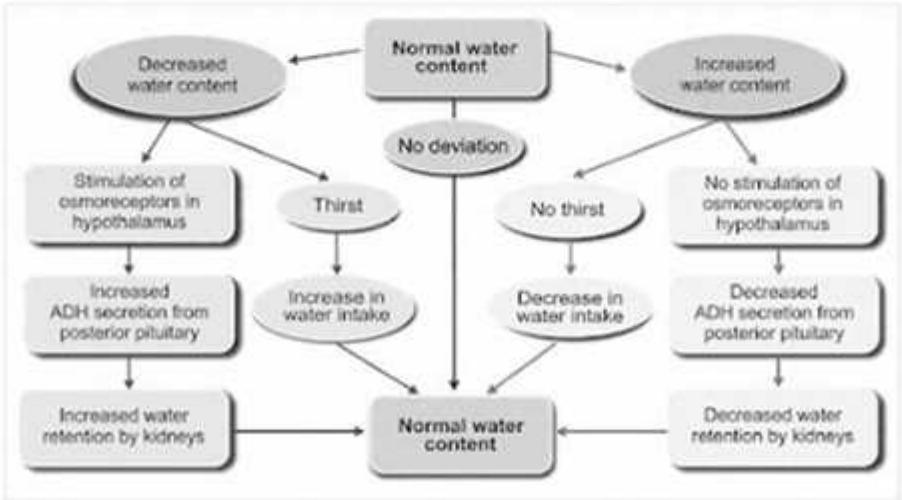


FIGURE 4.3: Negative feedback mechanism – maintenance of water balance.
ADH = Antidiuretic hormone.

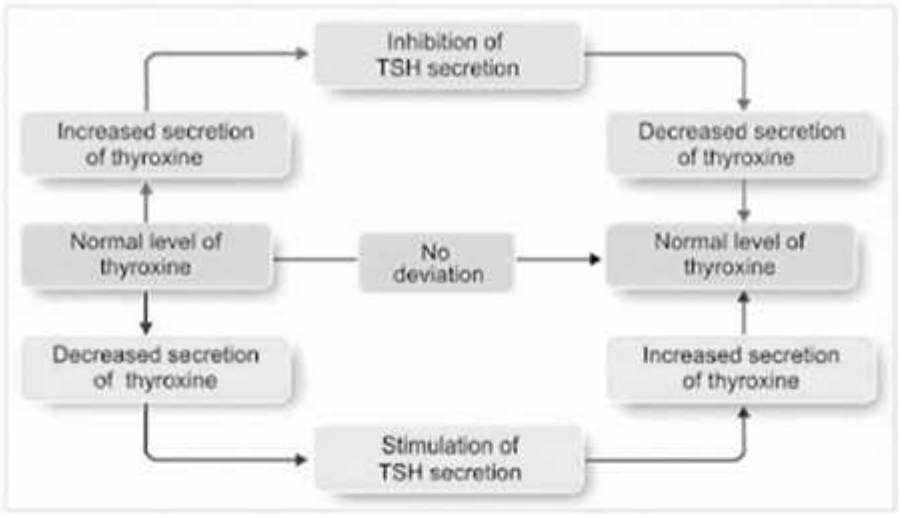
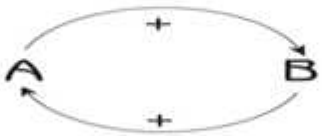


FIGURE 4.2: Negative feedback mechanism – secretion of thyroxine.
TSH = Thyroid-stimulating hormone.

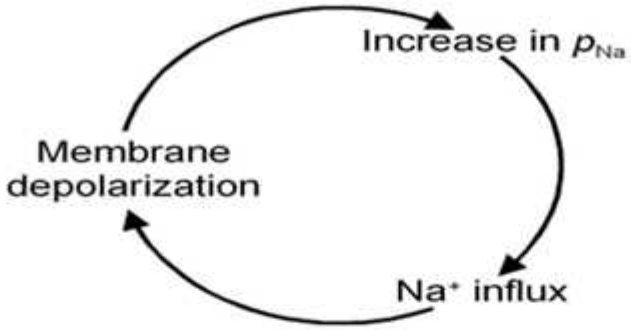
POSITIVE FEEDBACK

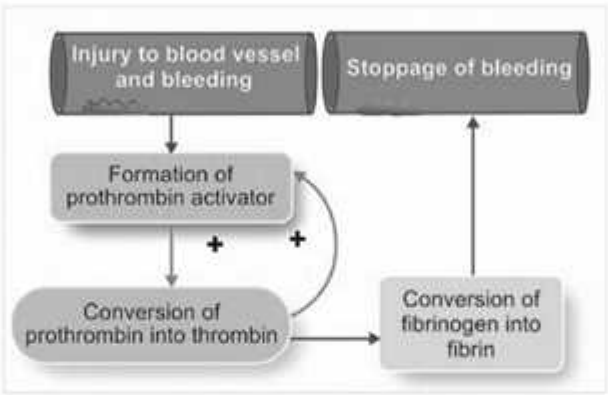
- Strengthens or reinforces a change.
- Makes abnormal values more abnormal.
- Produces 'Vicious Cycle'.
- But in body a mild degree of positive feedback can be overcome by the negative feedback control mechanisms of the body, and the vicious cycle fails to develop.



POSITIVE FEEDBACK LOOP

EXAMPLE: POSITIVE FEEDBACK MEMBRANE DEPOLARISATION





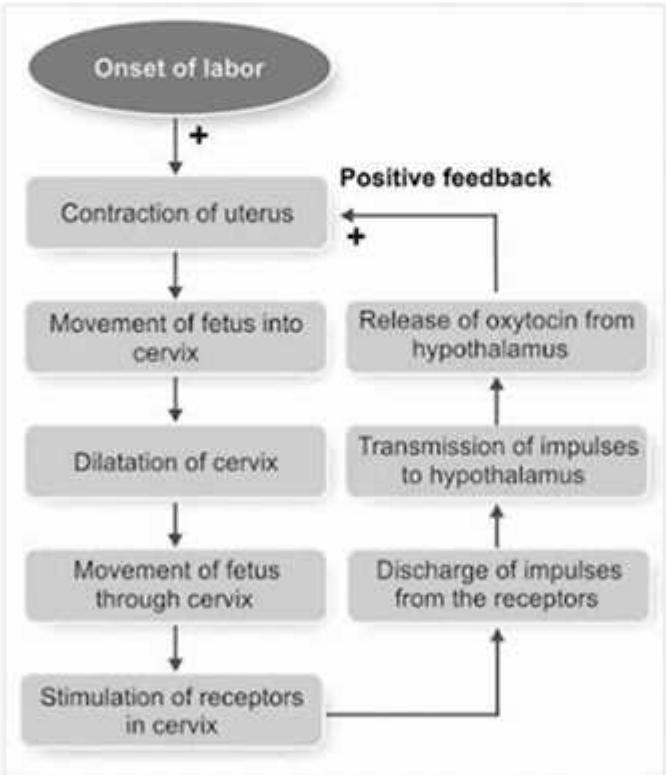


FIGURE 4.5: Positive feedback mechanism – parturition

POSITIVE FEEDBACKS IN BODY

- Action potential

- Clotting of blood
- Parturition
- Release of calcium from SR
- Sexual arousal
- LH surge

Summary

- Homeostasis is involved in continuous monitoring of body's internal environment with respect to altering external environment
- Components of homeostasis are ESI (Effector, Sensor, Integrator)
- Internal environment is maintained by positive and negative feedback mechanisms
- Most of the homeostasis mechanisms involve negative feedback

Cell injury

Pathology derived from two Greek words - Pathos – Suffering, Logos Study

"Scientific study of structure and function of the body in diseases"

"Study of disordered function or breakdown of homeostasis in diseases"

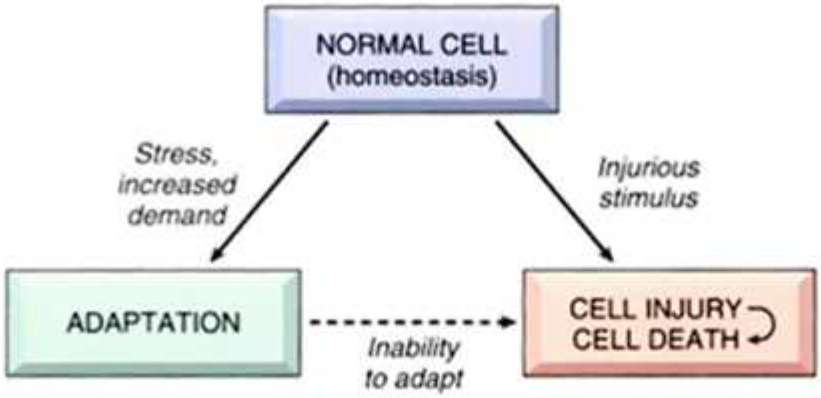
Basic Principles of Cell Injury and Adaptation

Cell injury - a variety of stresses a cell encounters as a result of changes in its internal and external environment

Cellular response to stress depends on

- Types of cells and tissues involved

Extent and type of cell injury



Etiology of cell injury

Cells may be broadly injured by two major ways:

A. By genetic causes

B. By acquired causes -

- Hypoxia and ischemia
- Physical agents
- Chemical agents and drugs
- Microbial agents
- Immunologic agents
- Nutritional derangements
- Psychological factors

Hypoxia and ischemia

- Deficiency of oxygen or hypoxia - failure to carry out activities
- Common cause of cell injury

Causes:

- Reduced supply of blood to cells (ischemia)
- Anemia, CO poisoning, cardio respiratory insufficiency and increased demand of tissues

Physical agents

- Mechanical trauma (e.g. road accidents)

- Thermal trauma (e.g. heat and cold)
- Electricity
- Radiation (UV and ionizing)
- Rapid changes in atmospheric pressure

Chemicals and drugs

- Chemical poisons such as cyanide, arsenic and mercury
- Strong acids and alkalis
- Environmental pollutants
- Insecticides and pesticides
- Oxygen at high concentration
- Hypertonic glucose and salt
- Social agents such as alcohol and narcotic drugs
- Therapeutic administration of drugs

Microbial agents

Infections caused by

- Bacteria
- Fungi
- Protozoa
- Metazoa
- Rickettsiae
- Virus
- Other parasites

Immunologic agents

- Immunity protects the host against various injurious agents

- May also turn lethal and cause cell injury

Examples -

- Hypersensitive reactions
- Anaphylactic reactions
- Autoimmune diseases
- Immunologic diseases

Nutritional derangements

Nutritional deficiency diseases of

- Overall deficiency of nutrients (starvation)
- Protein calorie malnutrition (kwashiorkor, marasmus)
- Minerals (anemia) or of trace elements
- Nutritional excess - obesity, atherosclerosis, heart diseases and hypertension

Psychological factors

- Mental stress
- Strain
- Anxiety
- Overwork
- Frustration
- Alcoholism
- smoking

Various forms of cellular responses to cell injury

Cellular adaptation

- Cell may adapt to the changes expressed morphologically
- Revert back to normal after the stress is removed

Reversible cell injury

- Mild to moderate stress; injured cells may recover

Irreversible cell injury

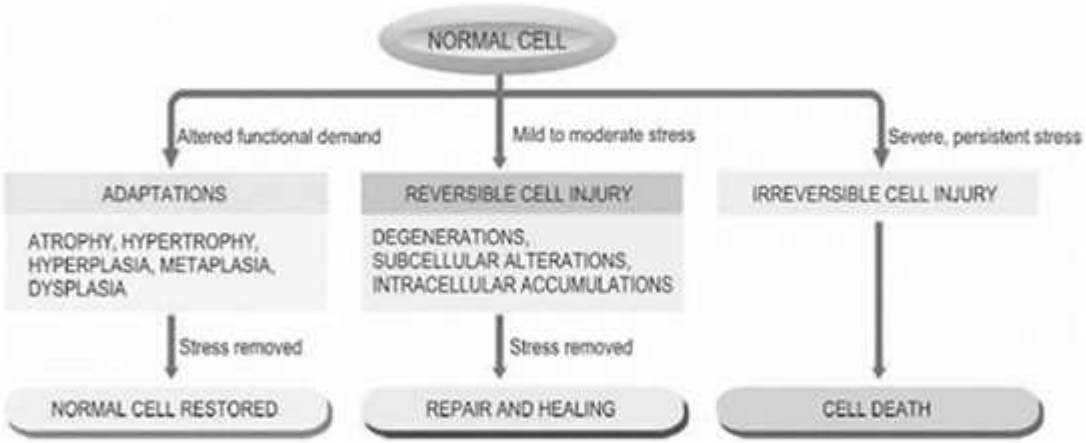
- Persistent injury; cell death may occur

Sub cellular changes

- Residual effect of reversible cell injury may persist in the cell
- Cell injury at sub cellular level

Intracellular accumulation

- Persistence of reversible cell injury; metabolites may accumulate in the cells



Cellular adaptation

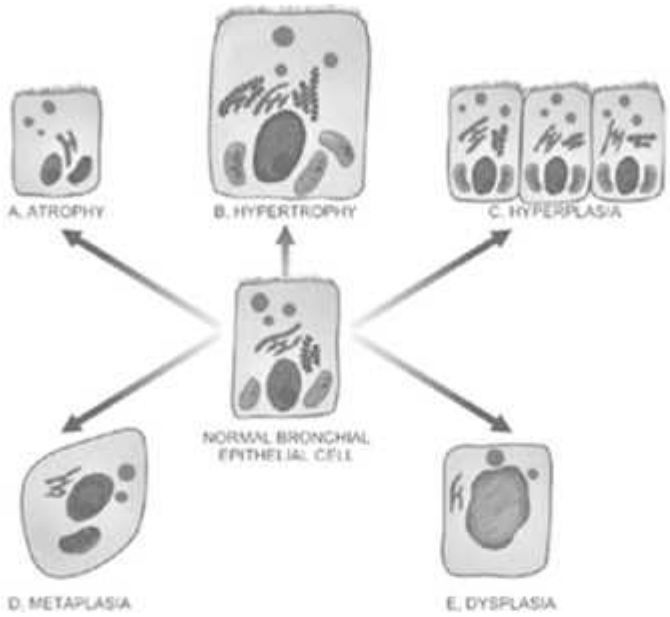
Atrophy

- Reduction of the number and size of parenchymal cells of an organ or its parts which was once normal

Causes –

Physiological cause or pathological cause

- Physiological atrophy
- Pathological atrophy

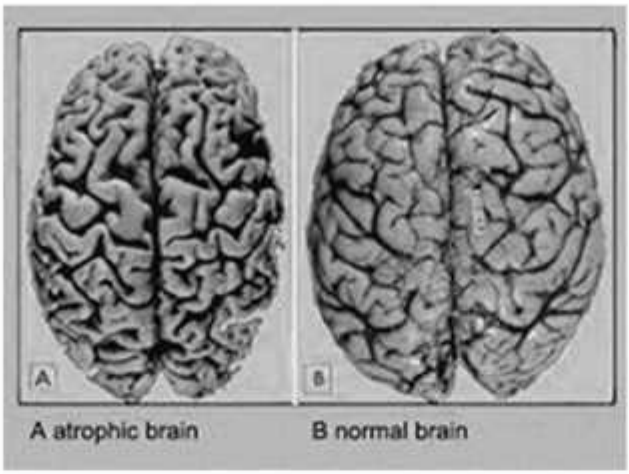


Physiologic atrophy

- Normal process of aging of some tissues
- Could be due to loss of endocrine stimulation or arteriosclerosis

Examples-

- Atrophy of –
- Lymphoid tissue in lymph nodes
- Gonads after menopause
- Brain



Pathologic atrophy

- Starvation atrophy
- Ischemic atrophy
- Disuse atrophy
- Neuropathic atrophy
- Endocrine atrophy
- Pressure atrophy

Hypertrophy

Increase in size of the parenchymal cells

Results in the enlargement of the organ or tissue

No change in number of cells

Causes:

- Physiologic or pathologic
  - By increased functional demand
  - Or hormonal stimulation

Physiologic hypertrophy

- Enlargement of uterus in pregnancy

Pathologic hypertrophy

- **Hypertrophy of heart -** Systemic hypertension Aortic valve disease Mitral insufficiency
- **Hypertrophy of skeletal muscles -** hypertrophised muscles in athletes and manual labourers

Hyperplasia

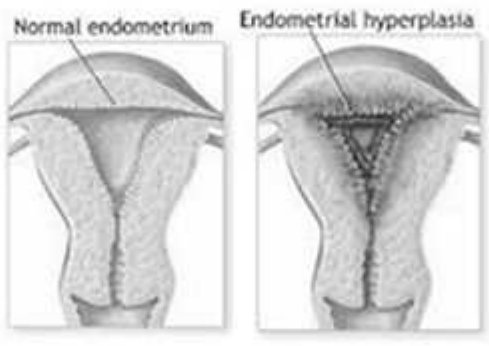
- Increase in number of parenchymal cells
- Enlargement of organ or tissue

Labile cells:

- Epithelial cells of skin and mucous membrane
    - Parenchymal cells of liver, pancreas, kidneys adrenals and thyroid
    - Nerve cells, heart muscles and skeletal muscles – less capacity

Physiological hyperplasia

- Female breast at puberty, pregnancy and lactation
- Pregnant uterus
- Prostrate hyperplasia in old age
- Compensatory hyperplasia – after hepatectomy

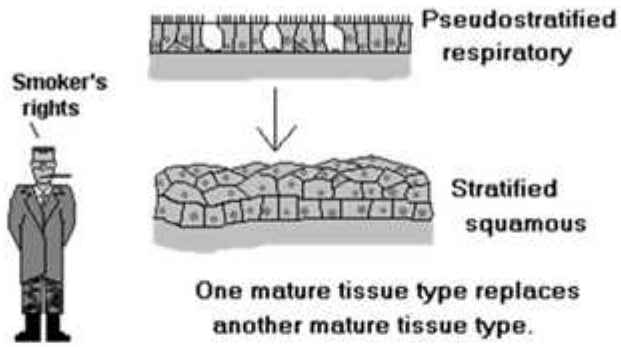


Pathological hyperplasia

- Endometrium following excess of estrogen
- Granulation tissue formation during wound healing

Metaplasia

- Irreversible change
- One type of epithelial or mesenchymal adult cell to another type of epithelial or mesenchymal cells
- Response to abnormal stimuli



Epithelial metaplasia

- In bronchus in chronic smokers
- Columnar metaplasia in Barrett's oesophagus, in which there is change of normal squamous epithelium to columnar epithelium

Mesenchymal metaplasia

- Cartilage of larynx and bronchi in elderly people
- Scar of chronic inflammation of prolonged duration
- Fibrous stroma of tumour

Dysplasia

- Disordered cellular development
- Accompanied with metaplasia and hyperplasia
- Referred to as *atypical hyperplasia*

Examples

- Increased number of layers of epithelial cells
- Disorderly arrangement of cells from basal layer to the surface layer

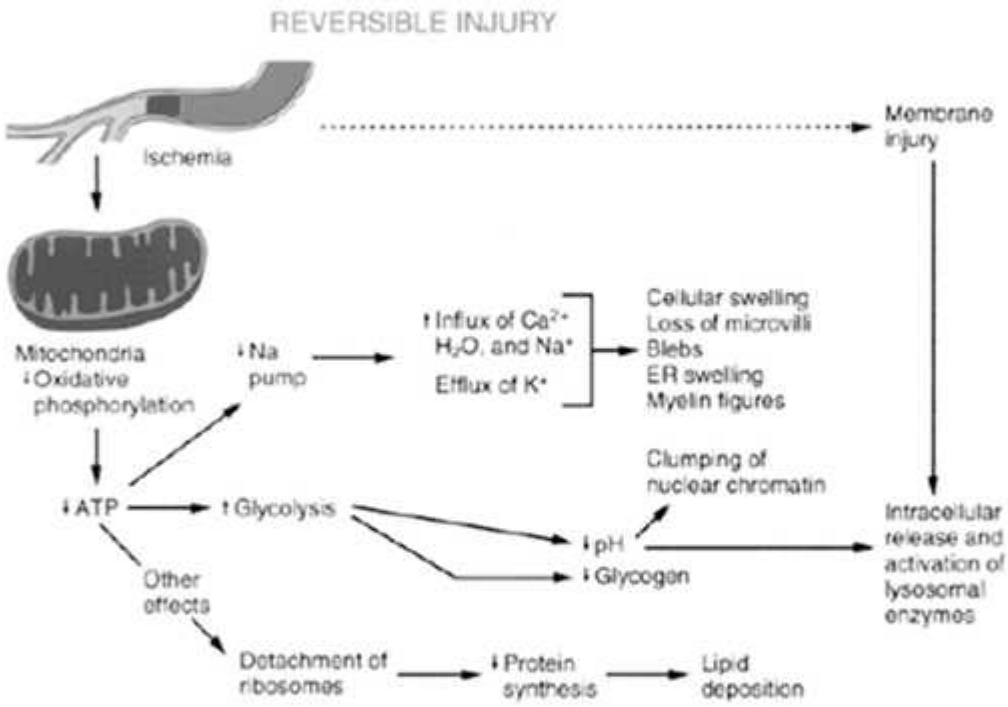
Summary

- Cell injury is the change in internal and external environment of cell due to variety of stress
- Cell responds to stress either by adaptation or undergoing cell injury
- Cell injury could be reversible or irreversible

Reversible cell injury

Pathogenesis of reversible cell injury due to hypoxia and ischemia

- If hypoxia and ischemia is for short duration, the effects are reversible



Sequence of changes occurring during reversible cell injury

- ↓ cellular ATP
- ↓ intracellular pH
- Damage to plasma membrane Na^+ pump
- ↓ protein synthesis
- Functional consequences
- Ultra structural changes

Decreased cellular ATP

- ATP required for – Membrane transport

  - Protein synthesis

- Lipid synthesis

- Phospholipids metabolism

- Source of ATP – Aerobic and anaerobic respiration
- Hypoxia and ischemia limits the supply of oxygen to cells, decreases ATP production

Decreased intracellular pH

- Low oxygen supply
- Aerobic respiration by mitochondria fails
- ATP generation by anaerobic glycolytic pathway
- Depletion of glycogen
- Accumulation of lactic acid
- Low pH of cell
- Acidosis and clumping of chromatin

Damage to plasma membrane sodium pump

- Na^+/K^+ ATP ase - operates at plasma membrane
- Allows active transport of Na^+ out of a cell

Diffusion of K^+ into cell after depolarization

- Low ATP affects Na^+ pump functioning
- Outward diffusion of K^+ ions
- Intracellular accumulation of Na^+
- Increased intracellular water - swelling of affected cell

Decreased protein synthesis

- Continuation of hypoxia
- Detachment of ribosome from granular ER
- Polysomes degraded to monosomes

- Decreased protein synthesis

Functional consequences

- Myocardial contractility ceases in 60 sec of coronary occlusion
- Reversed if circulation restored

Ultra structural changes

- Normal structure of ER is affected
- Membrane bound polyribosome detach from rough ER
- Swelling of mitochondria
- Myelin figures appear in cytoplasm
- Loss of microvilli
- Reduced synthesis of ribosomal RNA in nucleolus

Morphology of reversible cell injury

Reversible cell injury causes **cell degeneration**

<u>Cellular swelling</u>

- Due to influx of Na^+ ions & H_2O , escape of K^+
- Common causes - Bacterial toxins
  - Chemicals
  - Poisons
  - Burns
- Most affected organs – Kidney, Liver and Heart
- More vacoules appear
- ER dilates, ribosomes detach
- Mitochondrial swelling

Fatty changes

- Steatosis - Accumulation of fat within parenchymal cells
- Occurs common in liver
- In non – fatty tissues – heart skeletal muscles and kidney

Other changes

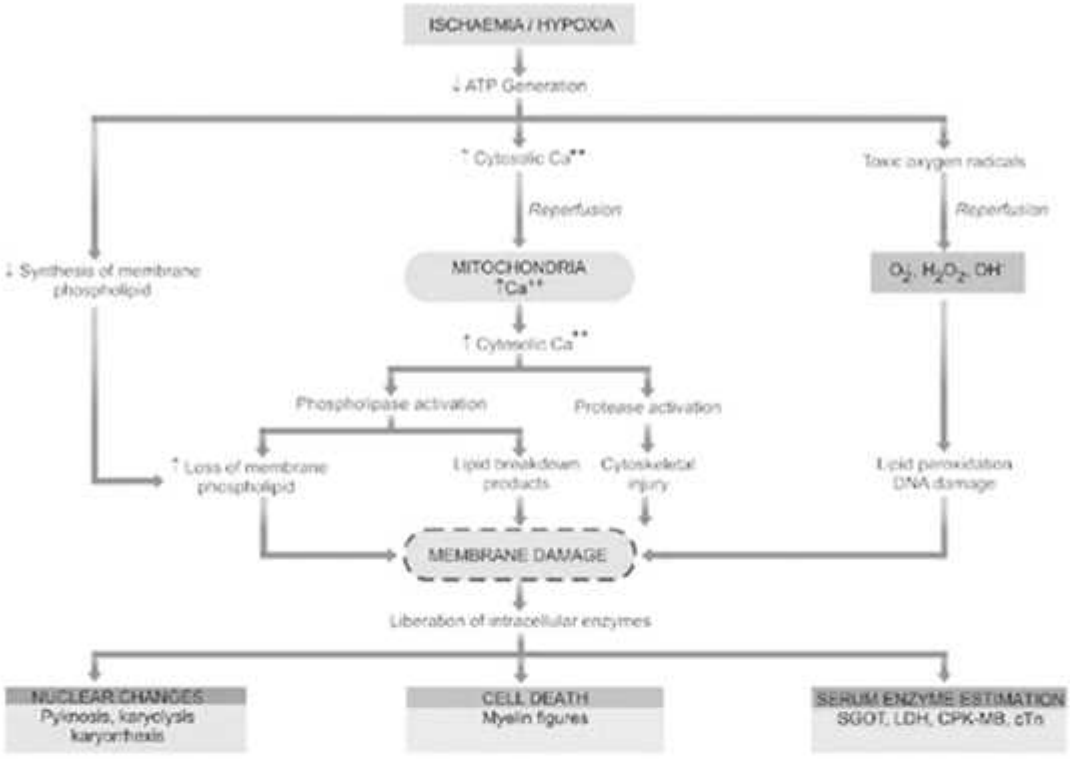
- Cytoskeletal changes
- Lysosomal changes
- Hypertrophy of smooth ER
- Intracellular accumulation of protein and glycogen
- Mitochondrial changes

Summary

- Hypoxia and ischemia causes cell injury
- If hypoxia and ischemia is for short duration, cell injury can be reversed
- Reversible cell injury brings about decreased cellular ATP, intracellular pH, damage to plasma membrane, decreased protein synthesis and ultra-structural changes
- Reversible cell injury causes cell degeneration

Irreversible cell injury

Pathogenesis of irreversible cell injury



- Ischemia & hypoxia persists for long time, results in irreversible changes in structure & function of cell

Irreversible cell injury differs from reversible cell injury

Inability of cell to reverse the mitochondrial changes

Disturbance in cell membrane structure & function

Sequence of events in irreversible cell injury

Mitochondrial dysfunction

- Continued hypoxia
- Large influx of Ca^{2+} - taken up by mitochondria - mitochondrial dysfunction
- Formation of vacuole
- Deposition of amorphous Ca^{2+} in mitochondrial matrix

Membrane damage

- O_2 deprivation - Ca^{2+} from mitochndria & ER shifts to cytosole
- ↑ Ca^{2+} activates phospholipases & proteases

- Phospholipases - breakdown phospholipids in cell membrane
- Accumulation of lipid break down product - Injury to cell
- Leakage of proteins, co-enzymes, RNA and other vital cell constituents
- Free radicals of O_2 - superoxide, hydrogen peroxide & hydroxyl
- Injury - lipid peroxidation, DNA, RNA destruction

Liberation of hydrolytic enzymes

- Damage to lysosomal membranes- liberates hydrolytic
- enzymes – digestion of cellular components
- Nuclear changes – cell death
- Cellular contents digested by lysosome hydrolases
- Dead cells replaced by myelin figues (large phospholipid masses)

Serum estimation of liberated intracellular enzymes

- Liberated enzymes leak across the abnormally permeable cell membrane in to serum
- Estimation of these enzyme levels in serum - extent of cell death

E.g. In MI, serum estimation of SGOT, LDH, Creatinine kinase and cardiac troponins – guides for assessing extent of death of cardiac muscles

Morphology of irreversible cell injury

Cell death occurs as local or focal changes

- Autolysis
- Necrosis
- Apoptosis and changes that follow like gangrene and pathological calcification

Autolysis

- Self digestion
- Disintegration of cell by its own hydrolytic enzyme
- Rapid in tissues rich in hydrolytic enzymes - pancreas, gastric mucosa

- Intermediate in liver, kidney and heart
- Slow in fibrous tissues
- May or may not be associated with inflammation

Necrosis

- Focal death of living tissue
- Progressive degeneration by various enzymes
- Often associated with inflammation
- Result of 2 concurrent process
  - Cell digestion by lytic enzymes
  - Denaturation of proteins

Types of necrosis

- Coagulative necrosis – Most commom, due to sudden cessation of blood supply
- Liquefaction necrosis – follows ischemic injury, bacterial or fungal infection; Common in brain

Caseous necrosis - combination of coagulative & liquefaction necrosis ; in centre of tuberculous infection

- Fat necrosis – focal area associated with fat destruction
- Fibrinoid necrosis – appearance of fibrin like materials; in peptic ulcer & immunologic injury

Gangrene

- Form of coagulative necrosis
- Characterized by inflammation
- Provoked by virulent bacteria resulting in massive tissue necrosis

3 types of gangrene

- Wet gangrene
- Dry gangrene
- Gas gangrene

Dry gangrene

- Usually occur in limbs
- Originates from toe or fingers
- Affected by improper blood supply due to ischemia
- Microbial contamination follows
- Spreads from origin upward until it reaches the point of blood supply

Wet gangrene

- Occurs in moist tissues and organs as mouth, bowel, lungs, cervix, etc.,
- Occur during vein blockage rather than arterial blockage

Gas gangrene

- Special form of wet gangrene
- Formed by gas forming clostridia - G +ve bacteria
- Gains entry into open wounds
- Produces toxins that causes necrosis and edema

Pathological calcification

- Deposition of calcium in tissues other than bone and enamel

e.g. Kidney stones

Two types

- **Dystrophic calcification-** Deposition of calcium in dead and degenerated tissue
- **Metastatic calcification -** In normal living tissues with deranged calcium metabolism

Apoptosis

- Co-ordinated, internally programmed cell death
- Physiological process - unwanted cells are eliminated

Changes occurring during apoptosis

- Shrinkage of cells

- Formation of membrane bound apoptotic body
- Condensation of chromatin
- Phagocytosis of apoptotic bodies by macrophages
- Proteolysis of cytoskeleto proteins

Necrosis vs. Apoptosis

Necrosis	Apoptosis
Evoked by non-physiological disturbances (immune reaction, microbes, hypoxia, ischemia & other poisons)	Non physiological process Induced by stimuli like lack of growth factor, change in hormonal environment
Significant inflammatory response	No inflammatory response
Affects group of cells	Affects individual cells
Loss of membrane integrity	Membrane blebbing, no loss of integrity
Begins with swelling of cytoplasm & mitochondria	Begins with shrinking of cytoplasm & condensation of nucleus
Ends with total cell lysis	Ends with fragmentation of cells in to smaller bodies
No vesicle formation, complete lysis	Formation of membrane bound vesicles, apoptotic body
Disintegration	Mitochondria becomes leaky due to pore formation
Passive process, no requirement of ATP	Energy dependent active process
Post lytic DNA process	Prelytic DNA fragmentation

Summary

- Hypoxia and ischemia causes cell injury
- If hypoxia and ischemia persists for a long time, it results in irreversible cell injury

- It is associated with mitochondrial dysfunction, membrane damage, liberation of hydrolytic enzymes

Irreversible cell injury brings about certain morphological changes like autolysis, gangrene, necrosis, apoptosis

Inflammation

"Local response of living mammalian tissues to injury due to any agent "

- Body defence reaction to eliminate or limit the spread of injurious agent, followed by removal of the necrosed cells and tissues
- Protective response

Etiology of Inflammation

- **Infective agents** - bacteria, viruses and their toxins, fungi, parasites
- **Immunological agents -** cell-mediated and antigen antibody reactions

Physical agents - heat, cold, radiation, mechanical trauma

Chemical agents - organic and inorganic poisons

Signs of inflammation

4 cardinal signs of inflammation

- Rubor (redness)
- Tumor (swelling)
- Calor (heat) and
- Dolor (pain)

Fifth sign - *functio laesa* (loss of function) - Virchow

Types of inflammation

Depending upon the defense capacity of host and duration of response

- Acute Inflammation
- Chronic inflammation

Acute Inflammation

- Short duration
- Represents early body reaction
- Followed by repair

Main features

- Accumulation of fluid & plasma at the affected site
- Intravascular activation of platelets
- Polymorpho nuclear neutrophills (PMN) – inflammatory cells

Chronic Inflammation

- Longer duration
- If causative agent of acute inflammation persists for long periods
- Recurrent attack of acute inflammation

Main features:

- Presence of lymphocytes, plasma cells & Macrophages as inflammatory cells

Changes in Acute inflammation

Two main events involved

1. Vascular events

- Alteration of microvasculature (arteries, capillaries & venules)

2. Cellular events

- Exudation of leucocytes
- Phagocytosis

Vascular events

- Alteration in the microvasculature - tissue injury

Haemodynamic Changes

Earliest features - vascular flow change, calibre of small blood vessels

1. Irrespective of the type of injury - transient vasoconstriction of arterioles

- Mild form – blood flow - 3-5 seconds
- More severe injury the vasoconstriction - 5 minutes

Vascular changes

2. Persistent progressive vasodilatation

- Mainly arterioles
- lesser extent - venules and capillaries
- Increased blood volume - redness and warmth

3. Progressive vasodilatation

- Elevate the local hydrostatic pressure - transudation of fluid into the extracellular space – swelling

4. Stasis of microcirculation

- Increased concentration of red cells - blood viscosity

5. Leucocytic margination

- Leucocytes stick to the vascular endothelium
- Move and migrate through the gaps between the endothelial cells into the extravascular space
- Emigration

Triple response

Flush

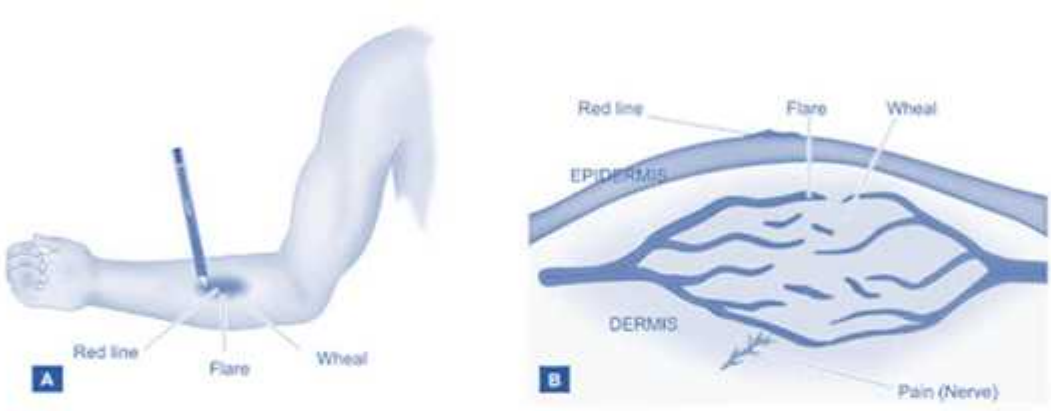
- Appearance of red line
- Local vasodilatation of capillaries and venules

Flare

- Bright reddish appearance or flush surrounding the red line
- Vasodilatation of the adjacent arterioles

Wheal

- Swelling or oedema of the surrounding
- Transudation of fluid into the extravascular space



Pathogenesis of altered vascular permeability

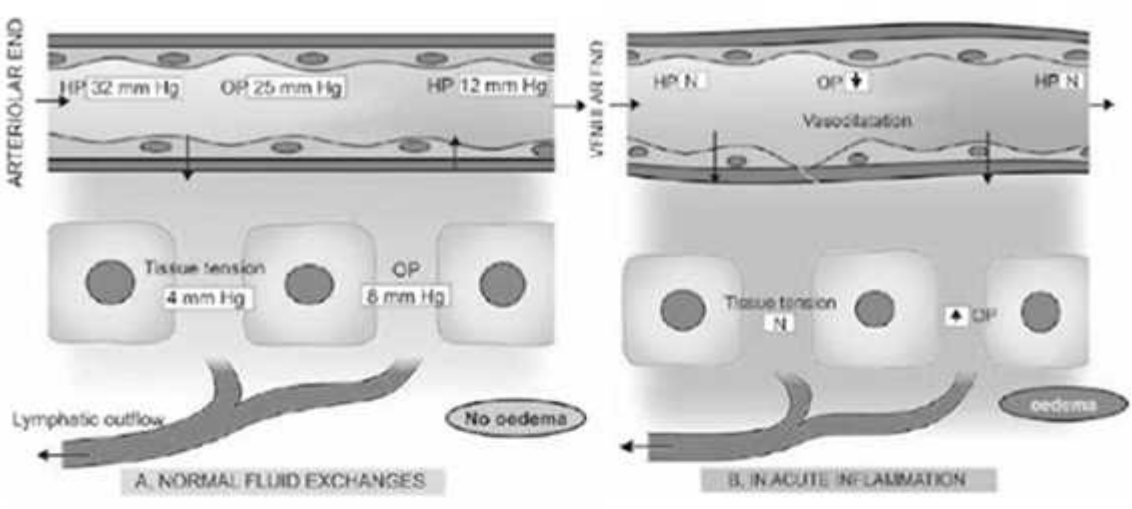
Normal circumstances - fluid balance - two opposing sets of forces that causes:

Outward movement of fluid from microcirculation

- intravascular hydrostatic pressure
- colloid osmotic pressure of interstitial fluid

Inward movement of interstitial fluid into circulation

- intravascular colloid osmotic pressure
- hydrostatic pressure of interstitial fluid



Contraction of endothelial cells

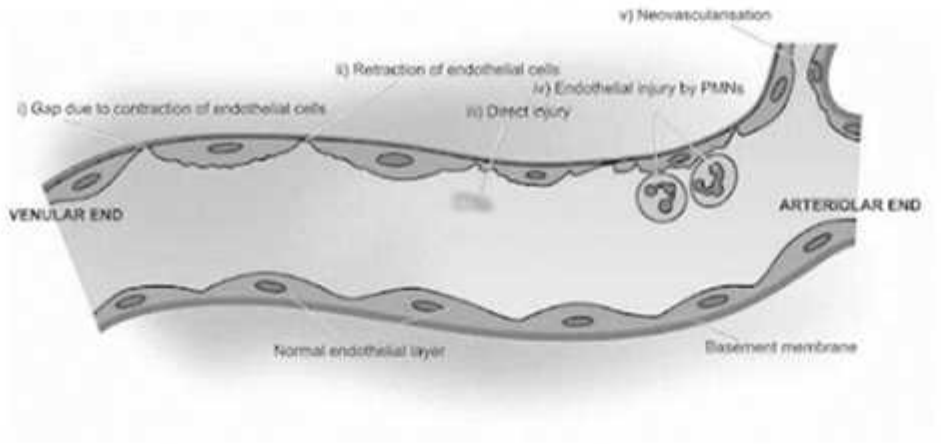
- Increased leakiness - venules exclusively
- Endothelial cells - temporary gaps – contraction - vascular leakiness - release of histamine, bradykinin and others
- Response - immediately after injury – reversible - short duration (15-30 minutes)
- Example: immediate transient leakage is mild thermal injury of skin of forearm

Retraction of endothelial cells

- structural re-organisation of the cytoskeleton of endothelial cells - reversible retraction – intercellular junctions – venules - cytokines such as interleukin-1 (IL-1) and tumour necrosis factor (TNF)-α - response takes 4-6 hours after injury - lasts for 2-4 hours or more
- The example invitro experimental work only

Direct injury to endothelial cells

- Cell necrosis, physical gaps at the sites of detached endothelial cell - thrombosis at site initiated
- Affects – microvasculature - immediately after injury last for several hours or days or delay of 2-12 hours and last for hours or days



Summary

- Inflammation is the local response of living mammalian tissues to injury due to any agent
- The four cardinal signs of inflammation are redness, swelling, heat and pain

Inflammation is of 2 type acute and chronic inflammation

Acute inflammation is of Shorter duration , represents early body reaction, followed by repair

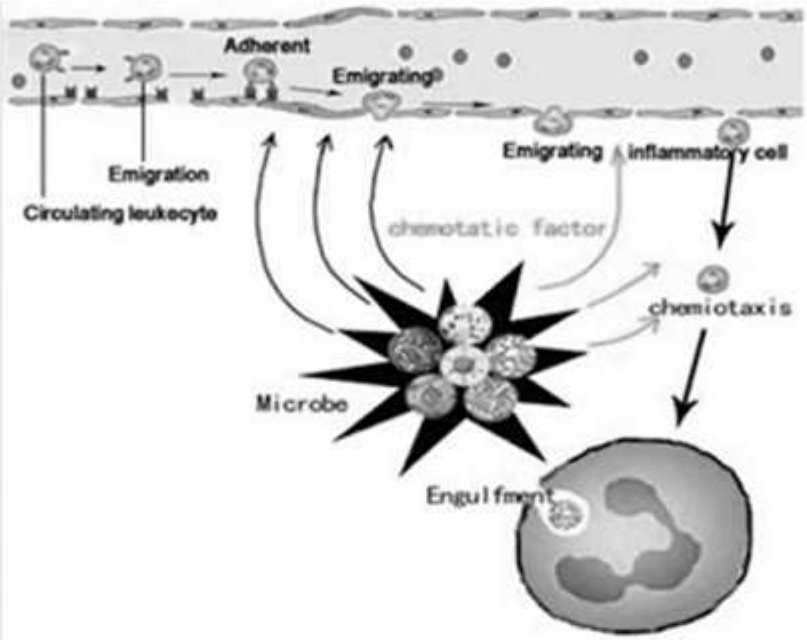
- Chronic inflammation is of longer duration and occurs when the agents remains for longer time
- Acute inflammation is characterized by cellular events and vascular events

Acute inflammation

Cellular events in acute inflammation

Cellular phases of inflammation comprises of two processes

- Exudation of leucocytes
- Phagocytosis



Cellular migration and phagocytosis

Exudation of leucocytes

1. Changes in the formed elements of blood

- Early stage of inflammation
- Increased rate of blood flow – vasodilatation - slowing or stasis of bloodstream
- Central stream of cells widens and peripheral plasma zone becomes narrower – exudation

Margination - redistribution - neutrophils of the central column come close to the vessel wall - pavementing

2. Rolling and adhesion:

Selectins – Helps rolling of neutrophills over endothelial cells

- P-selectin - rolling
- E-selectin - associated with both rolling and adhesion
- L-selectin - responsible for homing of circulating lymphocytes to the endothelial cells in lymph nodes

Integrins

- Activated during the process of loose and transient adhesions
- Between endothelial cells and leucocytes

- Stimulation receptors for integrins on the neutrophils
- Firm adhesion between leucocyte and endothelium

Immunoglobulin gene superfamily adhesion molecule intercellular adhesion molecule-1 (ICAM-1),

- Vascular cell adhesion molecule-1 (VCAM-1) – tighter adhesion and stabilise the interaction between leucocytes and endothelial cells
- Platelet-endothelial cell adhesion molecule- 1 (PECAM-1) or CD31 - leucocyte migration from the endothelial surface

3. Emigration and diapedesis :

- Sticking of neutrophils to the endothelium
- Movement along the endothelial surface
- Cytoplasmic pseudopods - cross the basement membrane – damage - collagenases - extravascular space - emigration
- Neutrophils are dominant first 24 hours
- Monocyte-macrophages - 24-48 hours

Diapedesis - passive phenomenon

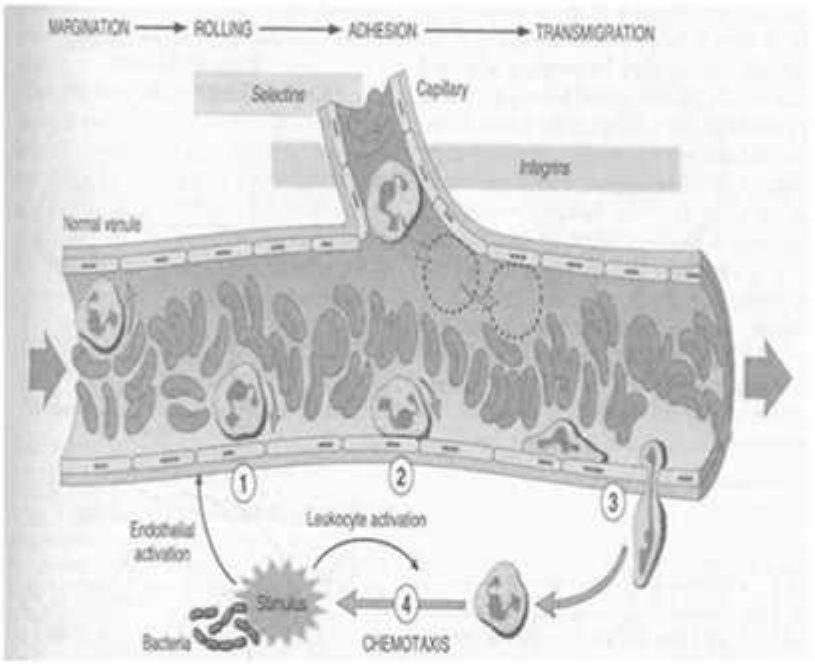
- RBCs being forced out
- Raised hydrostatic pressure
- Escape through the endothelial defects
- Diapedesis gives haemorrhagic appearance to the inflammatory exudate

4. Chemotaxis:

Chemotactic factor-mediate transmigration of leucocytes

- Leukotriene B4 (LT-B4)
- Components of complement system (C5a and C3a)
- Cytokines (Interleukins, in particular IL-8)
- Soluble bacterial products (such as formylated peptides)

Chemokines e.g. monocyte chemoattractant protein (MCP-1), eotaxin - eosinophils, NK cells- virally infected cells



Phagocytosis

Engulfment of solid particulate material by the cells - phagocytes

- Polymorphonuclear neutrophils (PMNs) - acute inflammatory response – microphages
- Circulating monocytes and fixed tissue mononuclear phagocytes - macrophages

Process involves 4 stages

- Recognition and attachment
- Engulfment
- Degranulation
- Killing and degradation

1. Recognition and attachment

- Phagocytes & microorganism – have similar charges
- Phagocytes covered with opsonin to facilitate bond
- IgG opsonin
- C_{3b} fraction of complement system

2. Engulfment

- After opsonisation, particle ready to be engukfed
- Cytoplasmic pseuodopods extend out from phagocytes
- Phagocytic vacuole
- Plasma membrabe enclosing phagocytic vacuole breaks
- Engulfed material lies free in cytoplasm
- Lysosome + Phagocytic vacuole = Phagolysosome

3. Secretion (Degranulation)

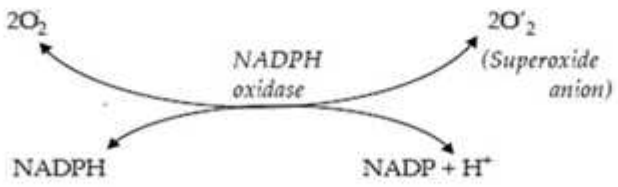
- Enzyme stored with in preformed granule are secreted into phagosome & extracellular environment
- Primary or azurophillic granules – fuse with lysosome
- Secondary or specific granules are discharged

4. Killing and degradation

Microorganisms - killed by antibacterial substances - degraded by hydrolytic enzymes

- Oxygen dependent bactericidal mechanism
- Oxygen independent bactericidal mechanism
- Nitric oxide

MPO-dependent killing:



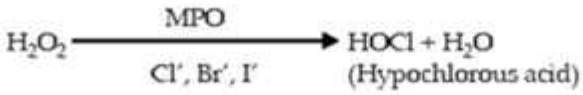
Superoxide is subsequently converted into H_2O_2 which has bactericidal properties:

$$2O'_2 + 2H^+ \longrightarrow H_2O_2$$

(Hydrogen peroxide)

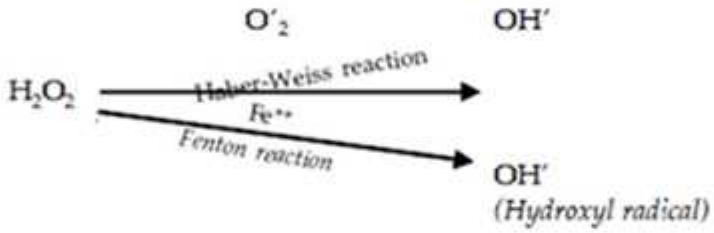
MPO-dependent killing:

- Enzyme MPO acts on hydrogen peroxide in the presence of halides to form corresponding **hypohalous acid – potent antibacterial**



MPO independent bactericidal mechanism

- Mature macrophages lack the enzyme MPO
- OH^{--} - Bactericidal activity



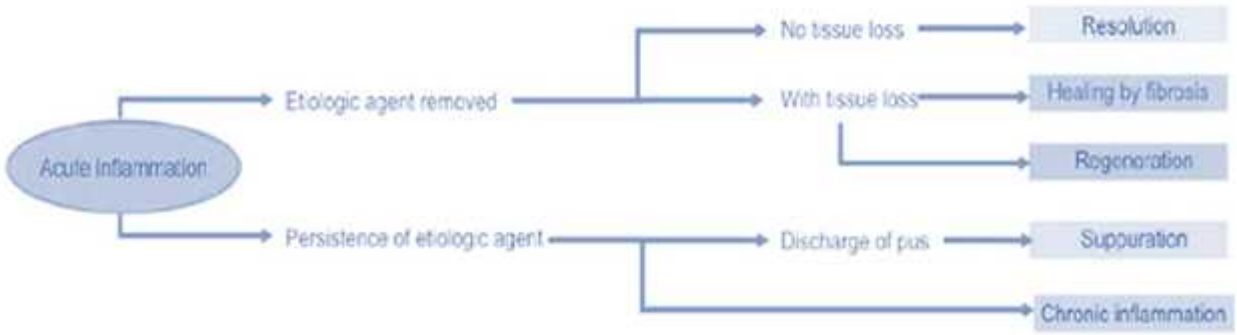
Oxygen independent killing bactericidal mechanism:

- Liberated lysosomal granules –
- lysis within phagosomes -
- lysosomal hydrolases,
- permeability increasing factors,
- cationic proteins (defensins),
- lipases, ptoteases, DNAases

Nitric oxide:

- Endothelial cells and activated macrophages
- Nitric oxide reactive free radicals - nitric oxide synthase – potent mechanism of microbial killing

Fate of acute inflammation

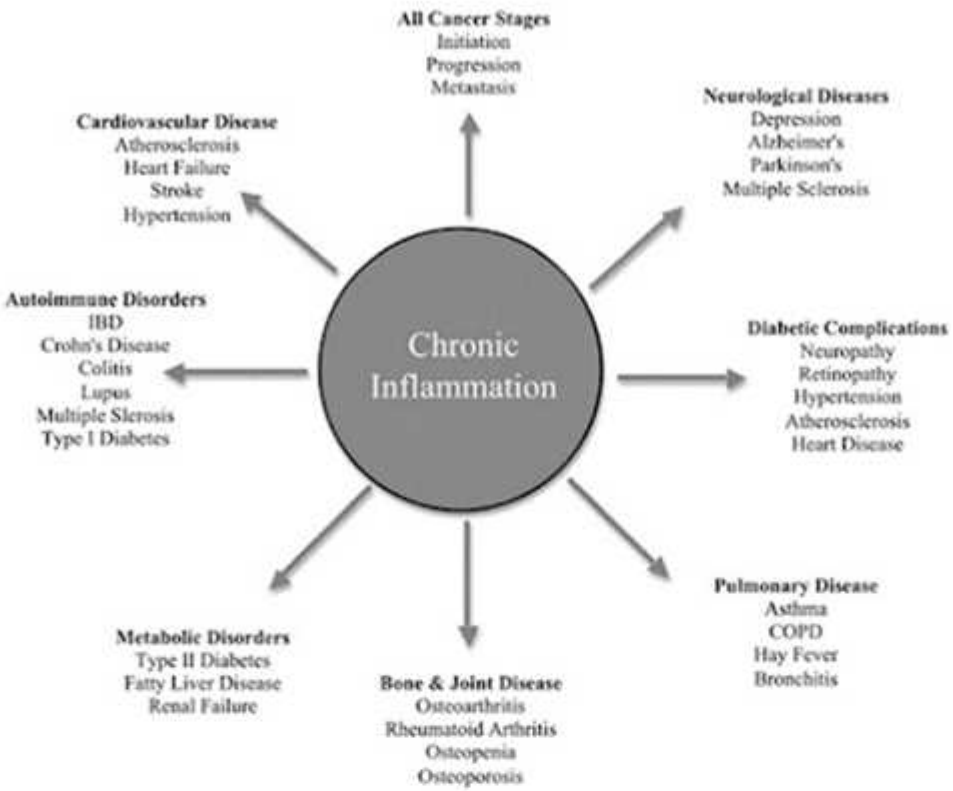


Summary

- Cellular phases of inflammation comprises of two processes -exudation of leucocytes and phagocytosis
- Exudation of leucocytes involves- changes in formed elements, rolling & adhesion, emmigration& diaphesis and invasion
- Phagocytosis involves cell eating
- Fate of acute inflammation may be healing, regeneration, suppuration or may develop into chronic inflammation

Chronic inflammation

Chronic inflammation is defined as prolonged process in which tissue destruction and inflammation occur at the same time



Chronic inflammation – Causes

1. Chronic inflammation following acute inflammation:

- Prolonged acute inflammation
- Tissue destruction is extensive
- The bacteria survive & persist in small numbers at the site of acute inflammation

e.g. Osteomyelitis, pneumonia terminating in lung abscess

2. Recurrent attacks of acute inflammation:

- Repeated attacks of acute inflammation
- Culminate in chronicity of the process

e.g. - Recurrent urinary tract infection leading to chronic pyelonephritis

– Repeated acute infection of gallbladder leading to chronic cholecystitis

3. Chronic inflammation starting de novo:

- Infection with organisms of low pathogenicity is chronic

e.g. infection with Mycobacterium tuberculosis.

General features of chronic inflammation

Mononuclear cell infiltration

Infiltration of chronic inflammatory lesions

- Phagocytes - circulating monocytes, tissue macrophages, epithelioid cells, multinucleated giant cells
- Lymphoid cells
- Chemotactic factors and adhesion molecules for continued infiltration of macrophages
- Local proliferation of macrophages
- Longer survival of macrophages at the site of inflammation

Tissue destruction or necrosis

- Brought about by activated macrophages
- Release a variety of biologically active substances

E.g. protease, elastase, collagenase, lipase, reactive oxygen radicals, cytokines (IL-1, IL-8, TNF-α), nitric oxide, angiogenesis growth factor

Proliferative changes

- Result of necrosis
- Proliferation of small blood vessels and fibroblasts is
- Formation of inflammatory granulation tissue
- Healing by fibrosis and collagen laying

Systemic effects of chronic inflammation

- Fever: mild fever, often with loss of weight and weakness
- Anaemia
- Leucocytosis
- ESR: elevated in all cases
- Amyloidosis: Long-term cases of chronic suppurative Inflammation - secondary systemic (AA) amyloidosis

Types of chronic inflammation

Non-specific

- Irritant substance - nonspecific chronic inflammatory
- Formation of granulation tissue
- Healing by fibrosis (chronic osteomyelitis, chronic ulcer)

Specific

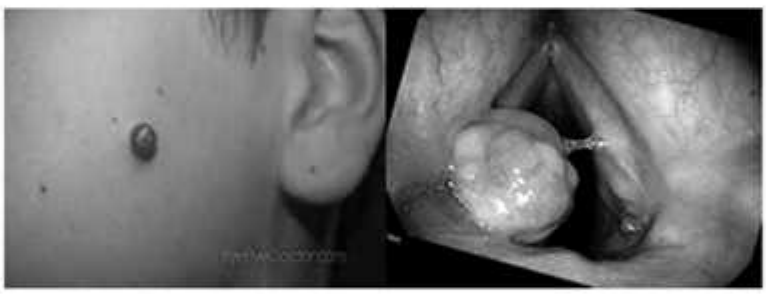
Injurious agent causes a characteristic histologic tissue response

e.g. tuberculosis, leprosy, syphilis

Granulomatous inflammation

Granuloma

- A tiny lesion about 1 mm in diamter
- Comprises of epitheloid cells in the centre & lymphoid in the periphery

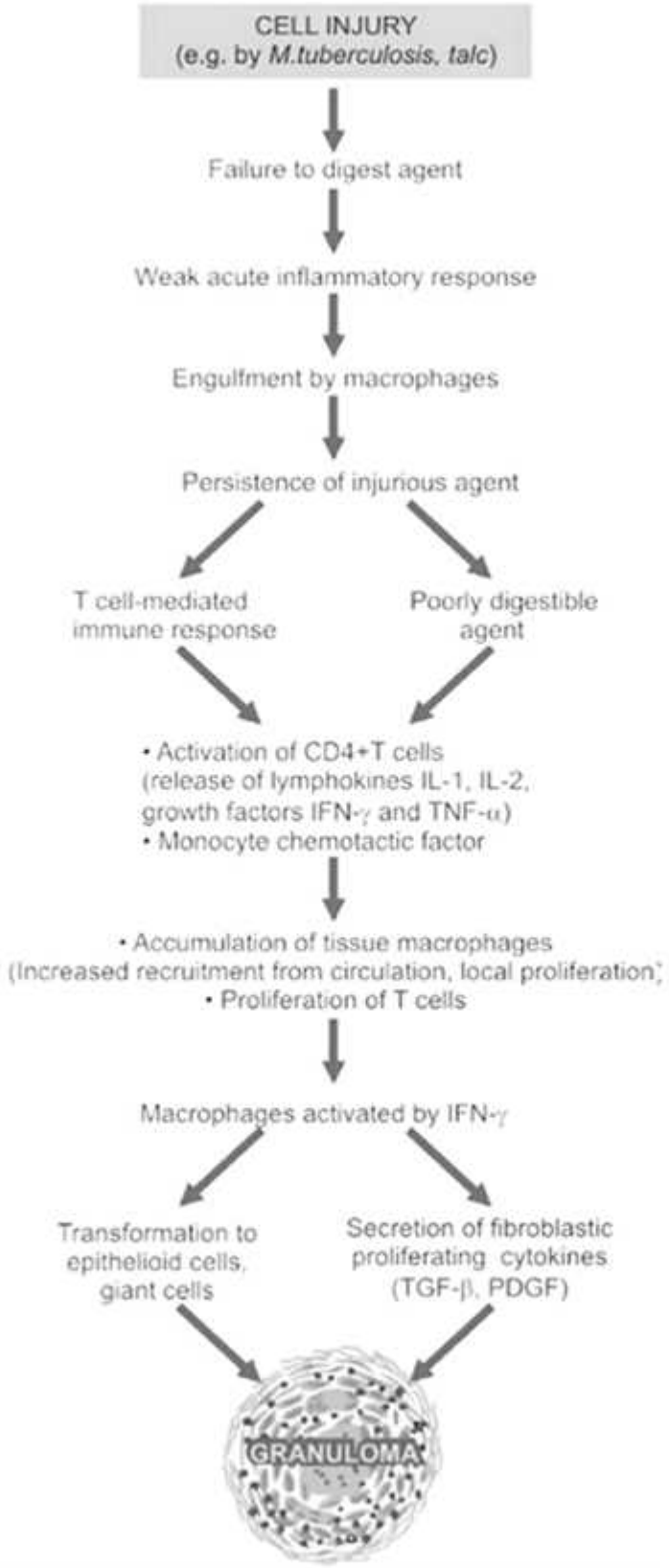


- Contains gaint cells
- Associated with necrosis & fibrosis
- Proliferation of fibroblast in the periphery
- Due to presence of micro organism

e.g. Mycobacterium tuberculosis

  - Poorly digestible
  - Cell mediated immune response

Pathogenesis of granulomatous inflammation

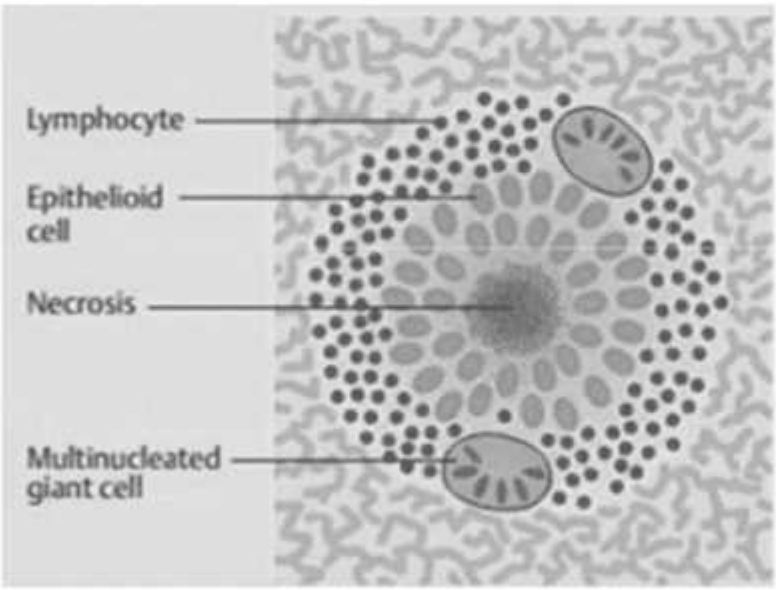


- Type IV hypersensitivity reaction
- Engulfment by macrophages

- Presentation of microbes to CD4+ T cells
- Activation of T-cells
- Cytokines

Composition of Granuloma

- Epithelioid cells
- Multinucleate giant cells
- Lymphoid cells
- Necrosis
- Fibrosis



Summary

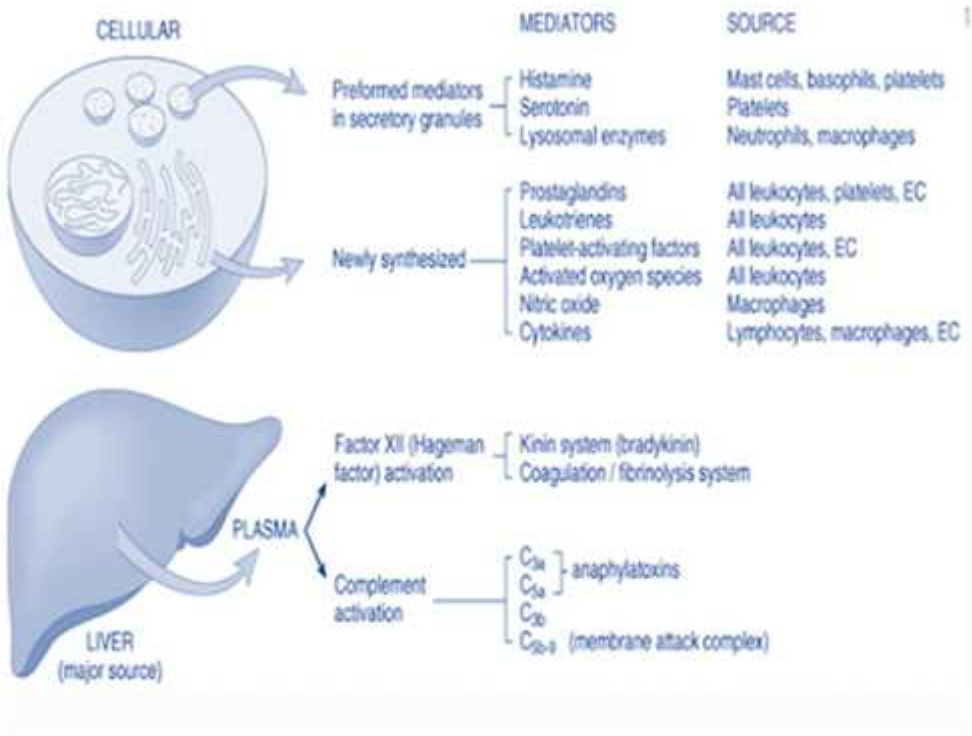
- Chronic inflammation is defined as prolonged process in which tissue destruction and inflammation occur at the same time
- Chronic inflammation may occur due to prolonged and recurrent attack of acute inflammation or may start *de novo*

Chronic inflammation is characterized by mononuclear cell infiltration, proliferation and necrosis

- Granulomatous inflammation occur by proliferation of fibroblast in the periphery due to presence of micro organism

Chemical mediators of inflammation

- Endogenous compounds
- Released during inflammation
- Increases vascular permeability
- Edema, Destruction of inflammatory agents



Cell derived mediators of inflammation

- Vasoactive amines – Histamine, Serotonin, Neuropeptides
- Arachidonic acid metabolites
  - Via COX pathway - Prostaglandins, Thromboxane A2, prostacyclin
  - Via LOX pathway - 5-HETE, leukotrienes
- Lysosomal system
- Platelet activating factor
- Nitric oxide and oxygen metabolites

Plasma derived mediators of inflammation

- The kinin system

- The clotting system
- The fibrinolytic system
- The complement system

Vasoactive amines (Autocoids)

Amine autocoids

- Histamine
- 5 – HT / Serotonin

Released within 1 hour of inflammatory response

Histamine

- Stored in mast cells, basophills & platelets

Released due to – Heat/cold radiations

  - Chemical irritant & immunological reactions
  - Anaphyla toxins

Main actions of Histamine

- Vaso dilation
- ↑ permeability of venules
- Itching & pain
- Release of other cell derived mediators
- Broncho constriction

Serotonin

- Present in chromaffin cells of GIT
- In spleen, nervous system, mast cells & platelets

Actions

- Vasodilation

- ↑vascular permeability
- Less potent than histamine

Neuropeptides

- Tachykinin neuropeptides - substance P, neurokinin A, vasoactive intestinal polypeptide (VIP) & somatostatin
- Produced in the central and peripheral nervous systems

Actions

- Increased vascular permeability
- Transmission of pain stimuli
- Mast cell degranulation

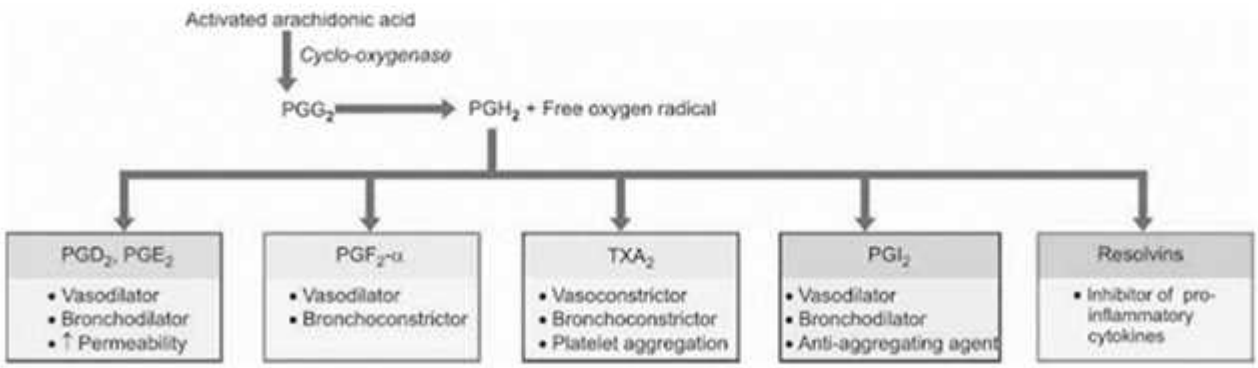
Arachdonic acid Metabolite

- Tissue injury – Phospholipase A_2 activation
- Conversion of phospholipids into arachdonic acid

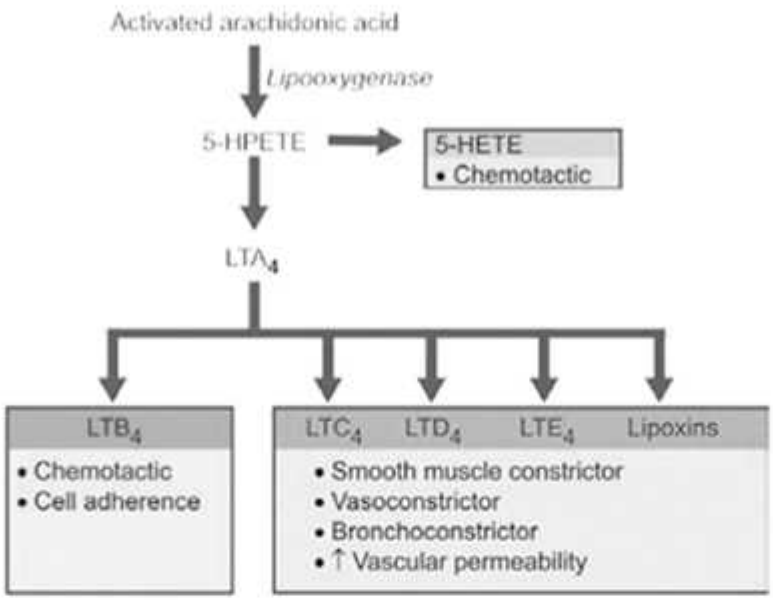
Metabolism of arachdonic acid follows 2 pathway

- COX (Cyclo-oxygenase) – Pathway
- LOX (Lipo- oxygenase) – Pathway

COX Pathway



LOX Pathway



Lysosomal components

Granules of Neutrophills

Primary granules

- Myeloperoxidase
- Acid hydrolase
- Neutral proteases

Secondary granules

- Lactoferrin
- Lysozyme
- Alkaline phosphatase
- Collagenase

Granules of Monocytes & Tissue macrophages

- Cells on degranulation releases mediators like
- Acid proteases
- Collagenase
- Elastase

- Plasminogen activator

More involved in chronic inflammation

Platelet Activating Factor (PAF)

IgE-sensitised basophils or mast cells, other leucocytes, endothelium and platelets

- ↑ vascular permeability
- Vasodilatation in low concentration and vasoconstriction
- Broncho constriction
- Adhesion of leucocytes to endothelium
- Chemotaxis

Cytokines

- Group of polypeptide substances
- Produced by activated lymphocytes/ monocytes
- Interleukin 1 & 8
- Tumor necrosis factor
- Interferon
- Platelet factor

Actions:

- IL –I, TNF α & β - ↑ leucocyte adherence, Platelet aggregation, proliferation of fibroblast
- Interferon gamma – activation of macrophages & neutrophils
- IL-8 – Chemotactic of neutrophills
- PF – 4 – Chemotactic for neutrophills, monocytes & eosinophills

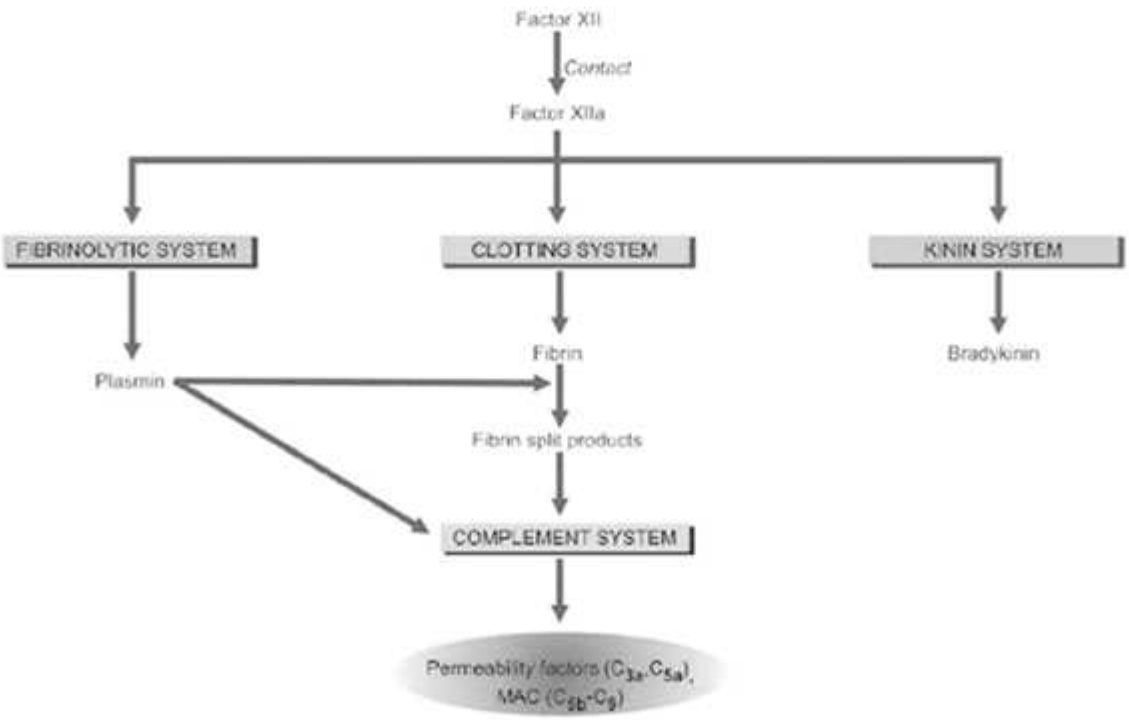
Nitric oxide & oxygen metabolites

- Released by activated macrophages from vascular endothelium
- Vasodilation

- Inhibiton of platelet aggregation
- Killing of micro organism
- O_2 free radicals released from activated neutrophills & macrophages
- Endothelial damage
- ↑vascular permeability
- Tissue matrix damage

Plasma derived mediators

- Interlinked system
- Include
  - Clotting system
  - Kinin system
  - Fibrinolytic system
  - Complement system
- Hageman factor (Factor XII) – connects the other 4 system



Clotting system

- Results in formation of fibrinogen
- Thrombin converts fibrinogen to fibrin & fibrinopeptide
  - ↑ vascular permeability
  - Chemotaxis of leucocytes
  - Anticoagulant activity

Fibrinolytic system

- Activated by plasminogen
- Plasminogen activator – plasminogen – plasmin- breakdown of fibrin - fibrinopeptides or fibrin split products

Actions

- Activation of factor XII
- Splits complement fraction C3to C3a– permeability factor
- Degrade fibrin to form fibrin split products

Complement system

Involves 2 pathways

- Classic pathway through antigen-antibody complexes
- Alternate pathway via non-immunologic agents such as bacterial toxins, cobra venoms and IgA

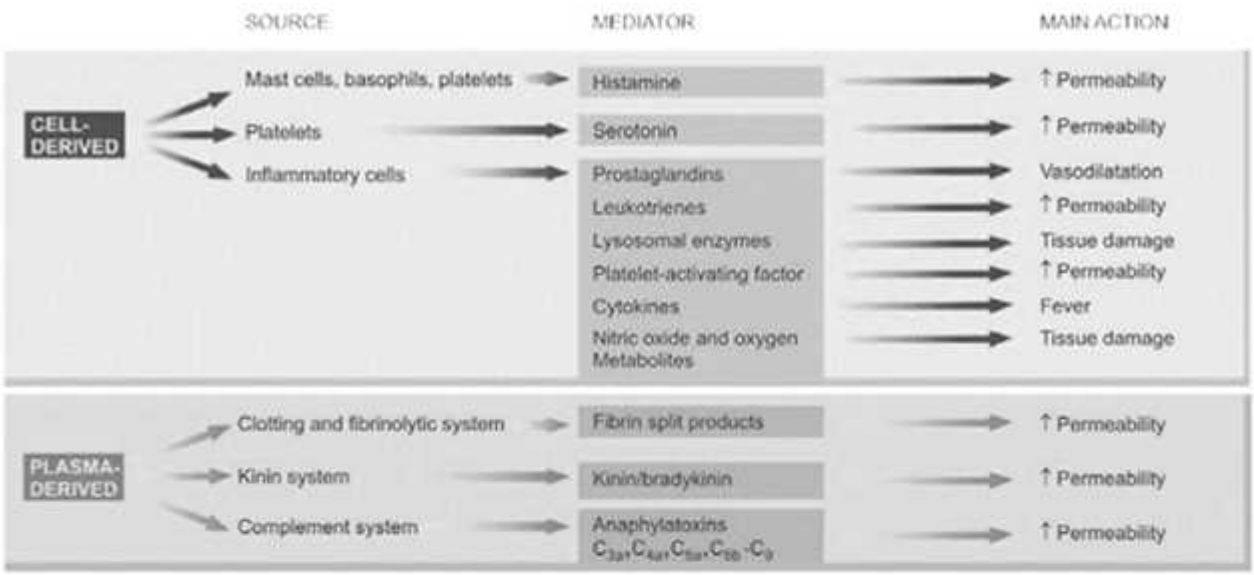
Anaphylatoxins (C3a, C5a, C4a)

- Activate mast cells and basophils to release of histamine
- cause increased vascular permeability
- augments phagocytosis

- C3b - an opsonin
- C5a - chemotactic for leucocytes

- Membrane attack complex (MAC) (C5b-C9) is a lipid dissolving agent and causes holes in the phospholipid membrane

Chemical mediators of inflammation



Summary

- Chemical mediators are endogenous compounds released during inflammation which increases vascular permeability, bring about edema and destruction of inflammatory agents

- Chemical mediators of inflammation are derived from cell and plasma

Cell derived mediators include histamine, serotonin, leukotrienes, platelet activating factors, cytokinines, prostaglandins

- Plasma derived mediators include kinin system, cltting and fibrinolytic system and clotting system

Wound Healing

Healing

- Healing - body response to injury

- An attempt to restore normal structure and function

- Involves **2 distinct** processes:

- Regeneration - healing by proliferation of parenchymal cells ; results in complete restoration

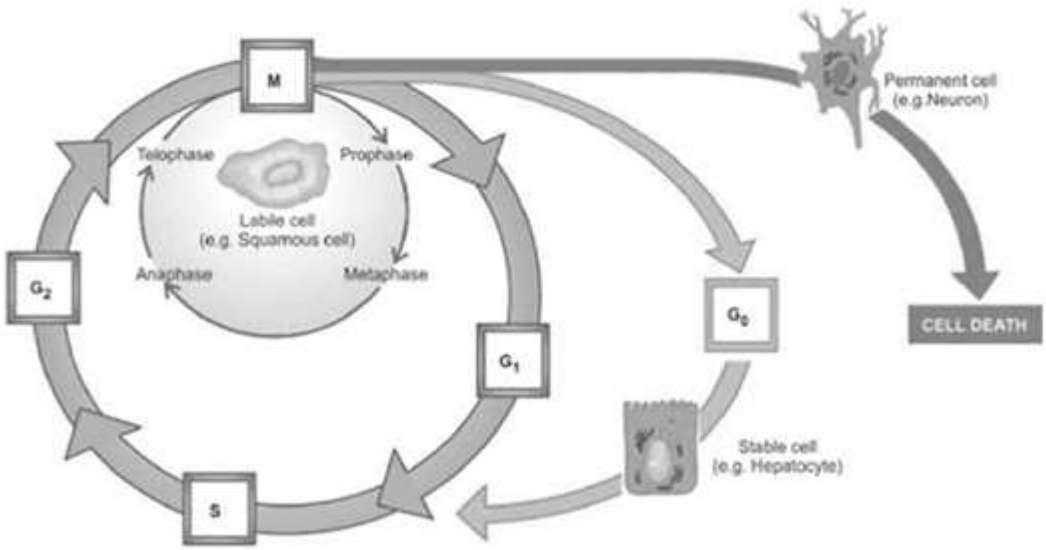
- Repair - healing by proliferation of connective tissue elements resulting in fibrosis and scar

Regeneration

- Proliferation of parenchmal cells
- Complete restoration of original tissue
- Cells are under the constant regulatory control of their cell cycle
- Involves
  - Epidermal growth factor
  - fibroblast growth factor, platelet derived
  - growth factor, endothelial growth factor,
  - transforming growth factor-β

Cell cycle and its phases

- Period between two successive cell divisions
- M (mitosis) phase: Phase of mitosis.
- G1 (gap 1) phase: daughter cell enters G1 phase after mitosis
- S (synthesis) phase: the synthesis of nuclear DNA
- G2 (gap 2) phase
- G0 (gap 0) phase: resting phase of the cell after an M phase



Phases of cell cycle

Type of cells involved in regeneration – depending on the speed of cell division

- Labile cells - continuously dividing
    - Epidermis, mucosal epithelium, GI tract epithelium etc
- Stable cells - low level of replication
    - Hepatocytes, renal tubular epithelium, pancreatic acini
- Permanent cells - never divide
    - Nerve cells, cardiac myocytes, skeletal muscle

Tissue Repair

- Replacement of injured tissue by fibrous tissue

Two processes are involved in repair:

1. Granulation tissue formation

2. Contraction of wounds

- Involves mesenchymal cells
- connective tissue cells
- endothelial cells, macrophages & some parenchymal cells

Granulation tissue formation

Phase of inflammation

- Acute inflammatory
- Response with exudation of plasma, neutrophils
- Monocytes within 24 hours

Phase of clearance

- Proteolytic enzymes liberated from Neutrophils
- Autolytic enzymes from dead tissues cells
- Phagocytic activity of macrophages
- Clear off the necrotic tissue, debris and RBCs

Phase of ingrowth of granulation tissue

1. Angiogenesis

- Proliferation of endothelial cells
- Development of capillary sprout
- Vascular endothelial growth factor (VEGF)
- Platelet-derived growth factor (PDGF)

2. Fibrogenesis

- Fibroblasts originate from fibrocytes
- Collagen fibrils begin to appear by about 6th day
- Formation of inactive looking scar - cicatrisation

Contraction of wounds

- Wound starts contracting after 2-3 days
- Process is completed by the 14th day
- Reduced by approximately 80% of its original size
- Results in rapid healing
- Dehydration
- Contraction of collagen
- Appearance of Myofibroblasts

Healing of wound in skin

- Combination of Regeneration and repair

Accomplished in one of the following two ways:

- Healing by first intention *(primary union)*
- Healing by second intention *(secondary union)*

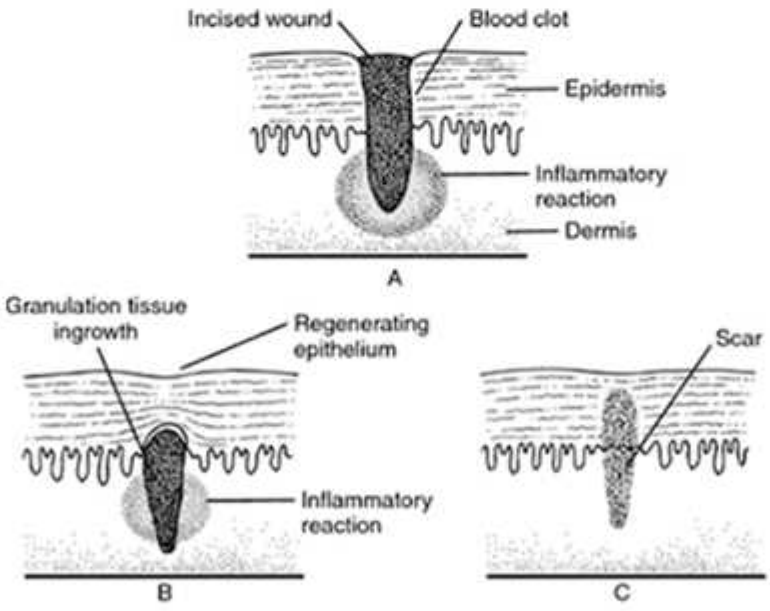
Healing by first intention *(primary union)*

Characteristics

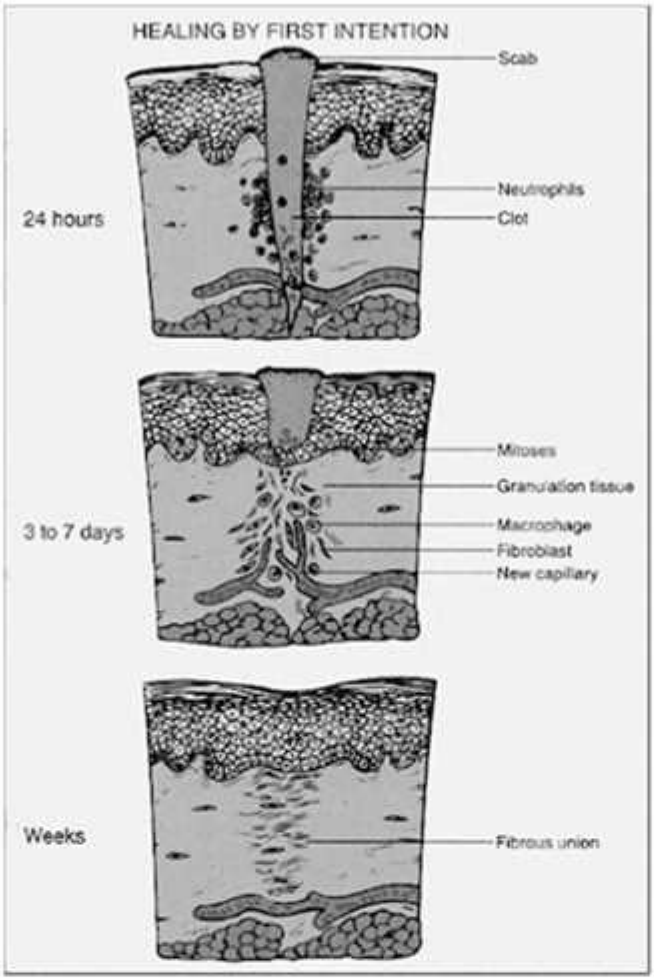
- Clean and uninfected
- Surgically incised
- Without much loss of cells and tissue
- Edges of wound are approximated by surgical sutures

Sequence of events

- Initial haemorrhage
- Acute inflammatory response
- Epithelial changes
- Organisation
- Suture tracks



Healing by first intention



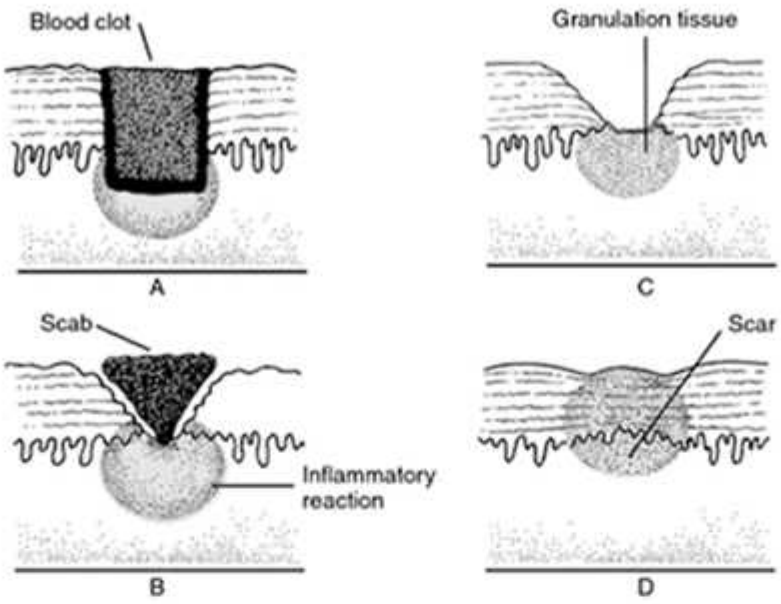
Healing by second intention *(secondary union)*

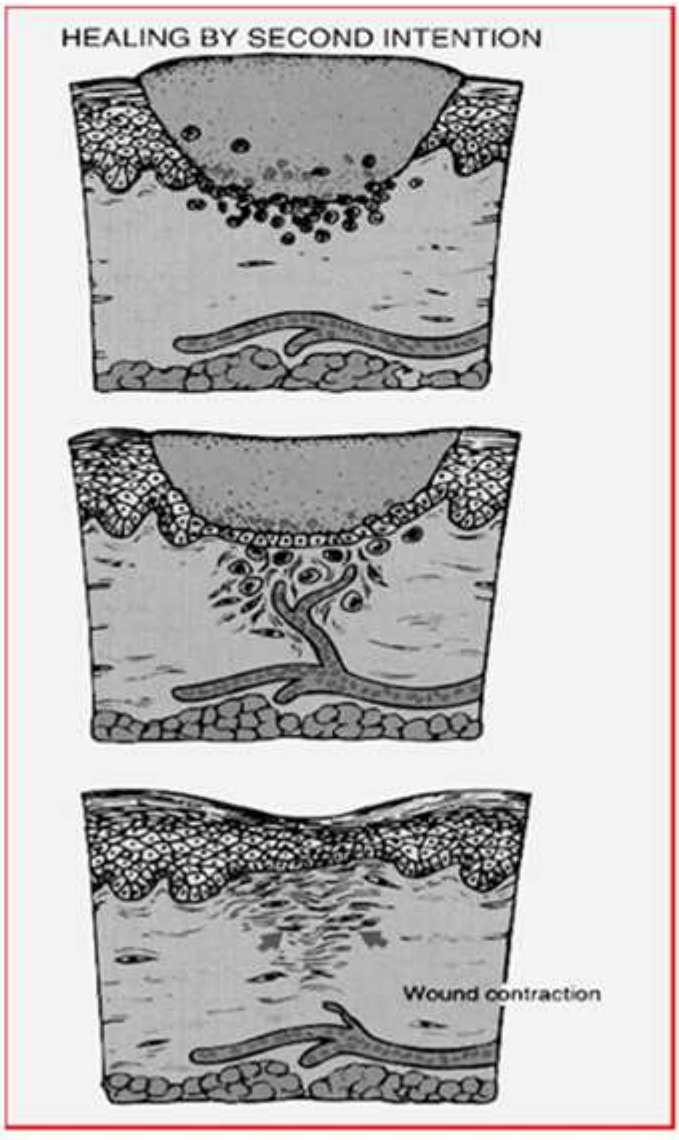
Characteristics

- Open with a large tissue defect, at times infected
- Having extensive loss of cells and tissues
- The wound is not approximated by surgical sutures but is left open

Sequence of events

- Initial haemorrhage followed by clotting
- Inflammatory phase – neutrophills & macrophages
- Epithelial changes – epidermal cell margination & proliferation
- Granulation tissue
- Wound contraction


Blood clot
A
Granulation tissue
C
Scab
Inflammatory reaction
B
Scar
D


HEALING BY SECOND INTENTION
Wound contraction

Factors affecting wound healing

Local factors

- Infection
- Blood supply to wound area
- Mechanical factors
- Foreign bodies
- Exposure to ionising radiation
- Size, Location & type of wound

Systemic factors

- Age
- Nutrition
- Systemic infection
- Uncontrolled diabetes
- Haemetological abnormalities

Summary

- Healing is a body response to injury it is an attempt to restore normal structure and function
- Healing occurs by two processes- regeneration and repair

Contraction of wound involves dehydration, contraction of collagen, appearance of myofibroblasts

- Healing of wounds of skin occurs by first intention or second intention depending on the type of infection

UNIT - II

Hypertension

Hypertension

Persistently **elevated arterial blood pressure** [BP]

Associated with both functional and morphologic alteration of blood vessels

2 types of arterial blood pressure

- Systolic BP (SBP)- achieved during cardiac contraction
- Diastolic BP (DBP)- achieved after contraction when the cardiac chambers are filling

SBP – DBP = pulse pressure (measure of arterial wall tension)

— Cardiac output - major determinant of SBP, Total peripheral resistance determines DBP

- Mean arterial pressure [MAP] - Average pressure throughout the cardiac cycle of contraction
- During cardiac cycle 2/3rd time spent in diastole and 1/3rd time in systole

MAP= [SBP (1/3)] +[DBP (2/3)]

BP= Cardiac output × Total peripheral resistance

Clinical classification of hypertension

Category	Systolic (mm Hg)	Diastolic (mm Hg)
Normal	< 130	<85
High normal	130-139	85-89
Hypertension		
• Mild (Stage 1)	140-159	90-99
• Moderate (Stage 2)	160-179	100-109
• Severe (Stage 3)	180-209	110-119
• Very severe (Stage 4)	≥ 210	≥ 120
Malignant hypertension	> 200	≥ 140

Etiological classification of hypertension

A. Primary essential hypertension

- Genetic factors
- Racial and environmental factors
- Risk factors modifying the course of HT

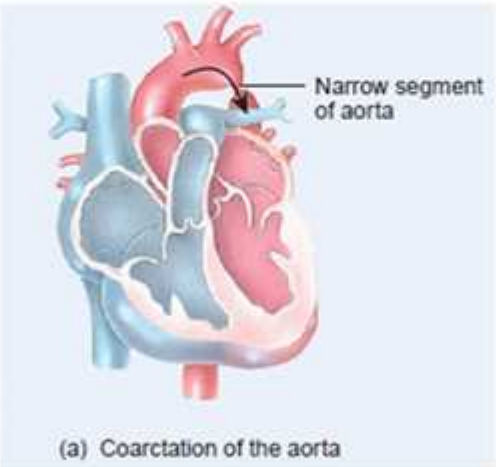
B. Secondary hypertension

- Renal – Renovascular

  Renal parenchymal disease
- Endocrine - Adrenocortical hyperfunction

  Hyperparathyroidism

  Oral contraceptives
- Contraction of aorta
- Neurogenic



(a) Coarctation of the aorta

Clinical classification of primary and secondary hypertension

Benign hypertension

- Observed in 95% of patients
- Slow rise in BP taking years to develop

Malignant/ accelerated hypertension

- Observed in 5-10% of patients
- Rapid rise in BP to 200/140 mm Hg or more
- If left untreated, patient's life expectancy decreases

Symptoms of Hypertension

When BP is severe, following symptoms are observed

- Nose bleeding
- Irregular heart beat
- Head ache
- Dizziness
- Fatigue
- Flushed face
- Breathing difficulties
- Strong tendency to uinate
- Vertigo, tinnitus, etc.,

Malignant hypertension is characterized by

- Pulsating headache beneath the eye
- Visual disturbance
- Nausea and vomiting
- Disturbed sleep

Pathogenesis of Hypertension

BP is the product of

- Cardiac output
- Total peripheral vascular resistance

- **Cardiac output**

  - Volume of blood that circulates through systemic blood vessels each minute

    - Dependent on stroke volume (SV)
    - SV - Volume of blood ejected by the left ventricle during each contraction

- Peripheral resistance depends on

  Viscosity of blood

  Diameter of the blood vessel

  Compliance

  - High viscosity - high pressure to pass through vascular bed
  - High pressure to pass through constricted and non-complaint blood vessels

BP is controlled by

- Neural component
- Peripheral auto regulatory mechanism
- Humoral mechanism
- Vascular endothelial mechanism

Neural component

- Both CNS & ANS controls BP

Centers in CNS are

Vasomotor center in Medulla

Vagal nucleus

Area postrema

Nuclues tractus solitarii

Maintenance of BP by sympathetic nervous system through α and β adrenergic receptors

++ post synaptic α_1 receptors — vasoconstriction — ↑ BP

++ pre synaptic α2 receptors — negative feedback on NA release

++ β_1 in heart — ↑ HR and contractility

++ β_2 in arterioles and venules — vasodilation

Change in BP senses by baro receptors in carotid artery and aortic arch

- Respond to change in arterial pressure
- Transmitted to brain through IX cranial nerve and vagus nerve
- ↑ discharge from barroreceptors − depression of vasomotor center − excitation of nucleus ambiguus − reverts change in BP

Peripheral auto regulatory mechanism

- Normal case – volume and pressure adaptive mechanism of kidney maintains BP

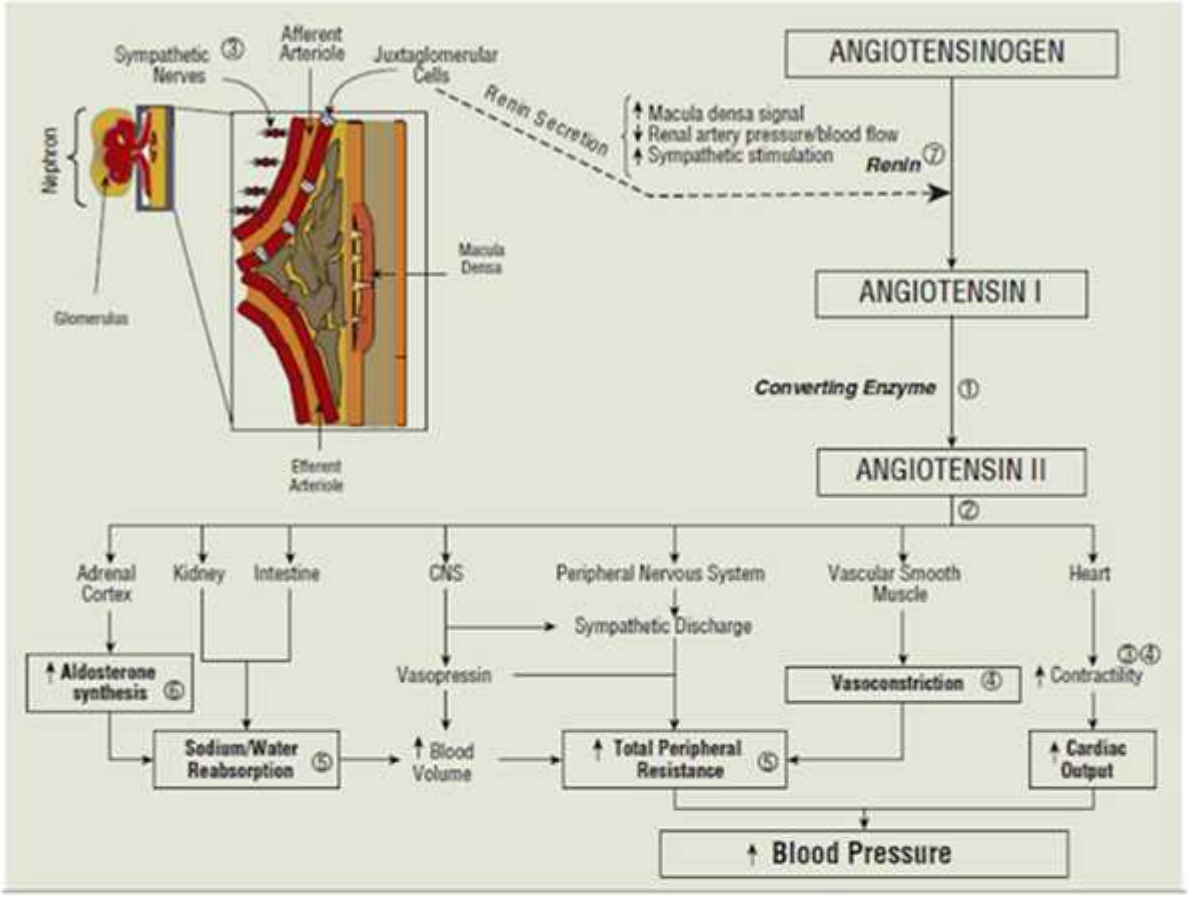
↓ BP – adaptation of kidney more Na^+ and H_2O retention

↑BP – adaptation of kidney Na^+ and H_2O excretion – ↓ blood volume & cardiac output

Humoral mechanism

- Renin Angiotensin Aldosterone system
- Natriuretic hormone
- Insulin resistance and hyperinsulinemia

Renin-Angiotensin-aldosterone system



Natriuretic hormone

- Inhibits Na^+/K^+ ATP ase
- Interferes with Na^+ transport across cell membrane
- ↑ Na^+ in body fluids - ↑ Natriuretic hormone - ↑ urinary excretion of Na^+ and H_2O
- Blocks active transport of Na^+ out of the walls of arterioles - ↑ vascular tone and BP

Insulin resistance and hyper insulinemia

- Causes Na^+ retention
- Increases sympathetic activity
- Increases vascular resistance
- Increases BP

Vascular endothelial mechanism

- Regulates blood vessel tone

- Vasodilating substances – Nitric oxide, Prostacyclin (PI_2) and bradykinin – Hypotension
- Vasoconstrictors – Angiotensin II and Endothelin I - ↑BP

Effect of dietary Na^+ Ca^{2+} K^+ on BP

- ↑ intra cellular Ca^{2+} - alters smooth muscle function on blood vessels - ↑ Peripheral vascular resistance
- K^+ depletion - ↑ Peripheral vascular resistance
- ↑ Na^+ in body fluids & in arterial wall - ↑ BP

Complications of Hypertension

- Blood vessels - Large arterioles dialatess

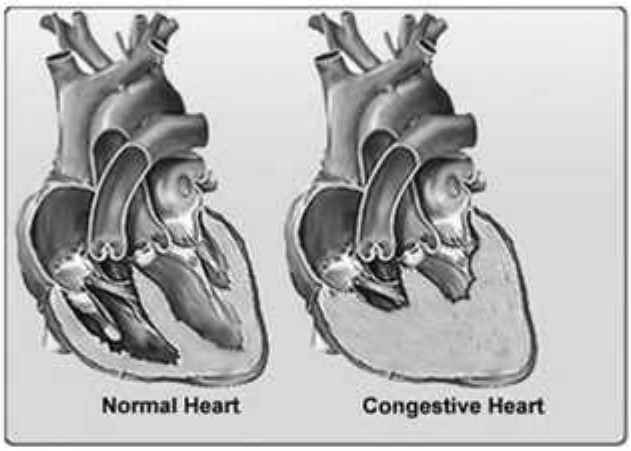
  - Smaller arterioles get damaged
- Eye – Arterial narrowing, haemmorhage
- Heart - Hypertropy of left ventricles, heart failure
- Kidney – Nephrosclerosis, renal damage, death in uremia
- Brain – Rupture of damaged blood vessels, encephalopathy, cerebral edema

Summary

- Persistently elevated arterial blood pressure is called hypertension
- Hypertension can be classified as benign or malignant or accelerated hypertension
- HT can also be classifies as primary and secondary HT based on etiology
- BP is controlled by neuronal component, humoral mechanism, peripheral autoregultory mechanism and vascular endothelial mechanism
- Any defects in the functioning of these mechanisms leads to the development of HT
- HT is affects kidneys, blood vessels, brain and predisposed to many cardiovascular diseases

CONGESTIVE CARDIAC FAILURE

- A clinical syndrome
- Result from any disorder that impairs the ability of the ventricle to fill with or eject blood
- Rendering the heart unable to pump blood at a rate sufficient to meet the metabolic demands of the body
- Heart failure can result from any disorder that reduces ventricular filling (diastolic dysfunction) and/or myocardial contractility (systolic dysfunction)



Etiology of Congestive Heart Failure

Systolic dysfunction (decreased contractility)

- Reduction in muscle mass (e.g. myocardial infarction)
- Dilated cardiomyopathies
- Ventricular hypertrophy
- Pressure overload (e.g. systemic or pulmonary HT, aortic or pulmonic valve stenosis)
- Volume overload (e.g., valvular regurgitation, shunts, high-output states)

Diastolic dysfunction (restriction in ventricular filling)

- Increased ventricular stiffness
- Ventricular hypertrophy (e.g. hypertrophic cardiomyopathy)
- Infiltrative myocardial diseases (e.g. amyloidosis, sarcoidosis, endomyocardial fibrosis)
- Myocardial ischemia and infarction

- Mitral or tricuspid valve stenosis
- Pericardial disease (e.g. pericarditis, pericardial tamponade)

Types of Heart Failure

- Acute and chronic heart failure
- High output and low output HF
- Left sided, right sided and biventricular HF
- Forward and backward HF
- Systolic and diastolic HF

Acute heart failure

- Heart is not able to pump the blood effectively
- Also called as Decompensated heart failure
- Compensatory mechanisms of human body cause increase in CO by stimulation of β_1 receptors and also RAA-system
- Both mechanism leads to vasoconstriction
- Treatment with **Inotropic** drugs becomes necessary

Chronic heart failure

- Failure of compensatory mechanism
- Heart needs to undergo surgery for its repair
- Further controlled by administration of drugs

High output HF:

- There is high demands of the body, which are not met even with increased cardiac output
- e.g.: anemia, pregnancy

Low output HF:

- There is decreased contractility of heart leading to decreased cardiac output
- e.g.: cardiomyopathy, valvular disease

Left sided (left ventricular) HF

- Excess fluid accumulates upstream
- Reduction in left ventricular output
- Increase in left atrial pressure
- Increase in pulmonary venous pressure

 Acute increase in left atrial pressure causes pulmonary congestion and pulmonary edema e.g.: MI

 Gradual increase in left atrial pressure causes reflex pulmonary hypertension but no pulmonary edema

e.g. : aortic stenosis

Right sided (right ventricular) HF:

- Excess fluid accumulates upstream behind the failing right ventricle
- Reduction in right ventricular output
- Results in systemic venous congestion

Ex: pulmonary valvular stenosis, multiple pulmonary emboli

Systolic HF:

- Characterized by an abnormality of ventricular contraction
- As seen in ischemic heart failure and dilated cardiac myopathy

Diastolic HF:

- Characterized by an impaired ventricular relaxation
- Increased ventricular stiffness resulting in diastolic dysfunction

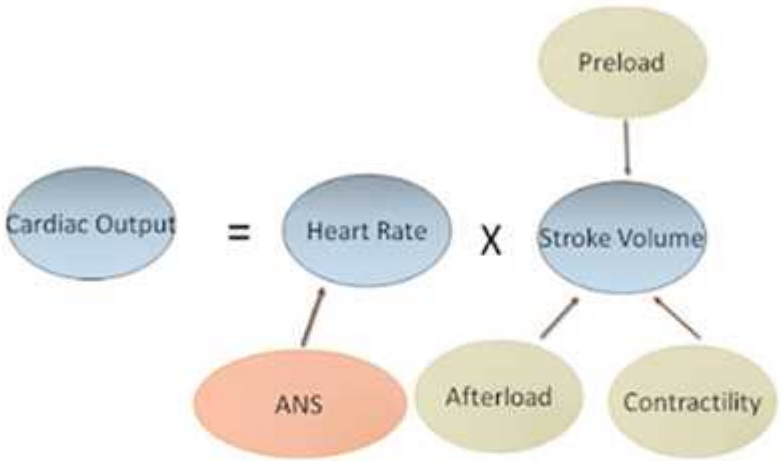
e.g.**:** ischemia, left ventricular hypertrophy

Pathophysiology of Congestive Heart Failure

Preload: Pressure that fills the left ventricle during diastole

- **Main Determinant**- left ventricular compliance and venous return
- Small increase in end-diastolic volume

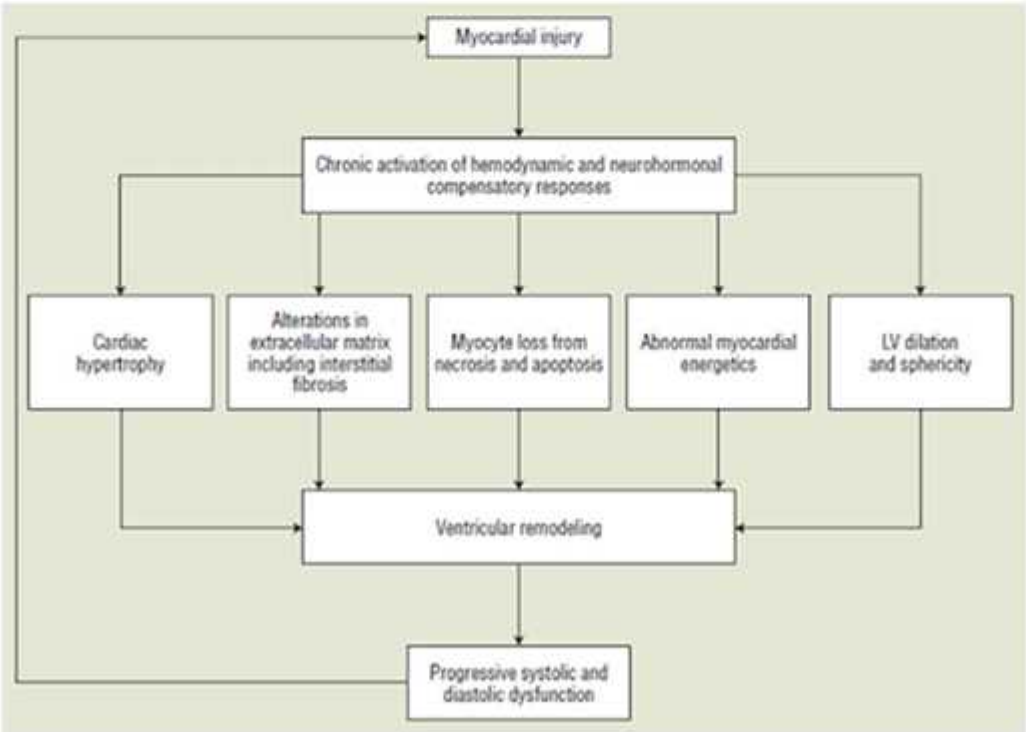
- large increase in cardiac output
- Primary compensatory mechanism in normal heart
- Ability of heart to alter the force of contraction depends on preload



Afterload: Pressure against which the left ventricular contracts and is measured as the mean aortic pressure

- Main determinants - total peripheral resistance and left ventricle size
- Left ventricular dysfunction - an inverse relationship exist between afterload and stroke volume
- An increase in afterload causes a decrease in stroke volume

Key components of the pathophysiology of cardiac remodelling



Compensatory Mechanisms

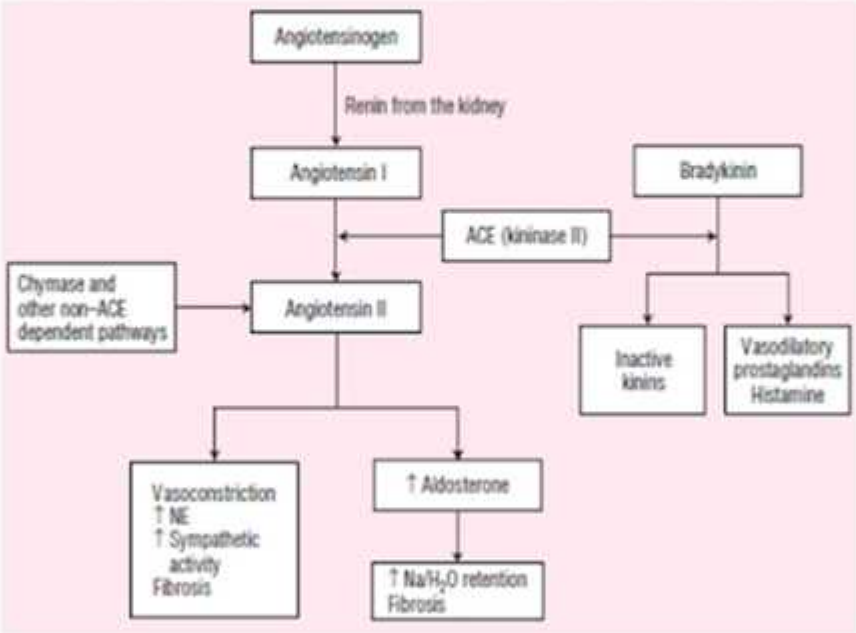
Cardiac compensatory mechanism:

- Ventricular dilation
- Ventricular hypertrophy

Peripheral compensatory mechanisms:

- Increased sympathetic activity
- Activation of renin angiotensin aldosterone system
- Increased release of arginine vasopressin

Renin Angiotensin Aldosterone system



Clinical Presentation – Signs of <u>Congestive Heart Failure</u>

- Pulmonary edema
- Pleural effusion
- Tachycardia
- Cardiomegaly
- Peripheral edema
- Jugular venous distension

- Hepatojugular reflux
- Hepatomegaly

Symptoms of Congestive Heart Failure

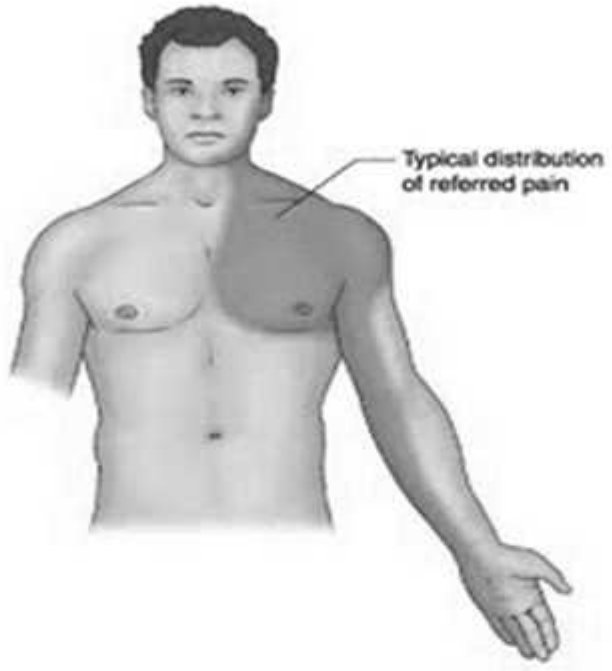
- Dyspnea
- Orthopnea
- Paroxysmal nocturnal dyspnea
- Exercise intolerance
- Tachypnea
- Ascites, Mental status changes
- Cough
- Fatigue
- Nocturia
- Hemoptysis
- Abdominal pain, Anorexia, Nausea, Bloating

SUMMARY

- CHF is a clinical syndrome that impairs the ability of the ventricle to fill with or eject blood
- Heart is unable to pump blood at a rate sufficient to meet the metabolic demands of the body
- It can be classified as: Acute and chronic heart failure,
- High output and low output heart failure,
- Left sided, right sided and biventricular heart failure,
- Systolic and diastolic heart failure

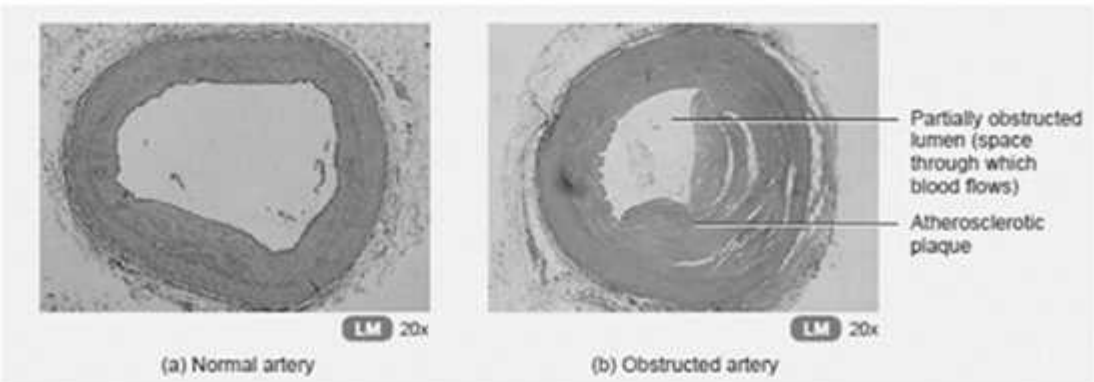
Angina pectoris

- Discomfort due to transient myocardial ischemia
- Heart muscle does not receive enough blood (nutrient & O_2) resulting in chest pain



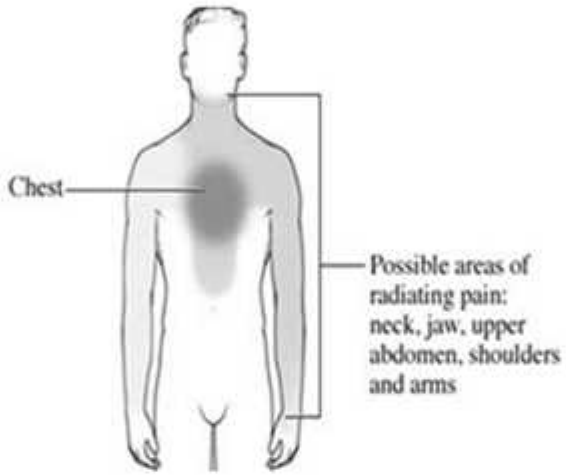
Etiology of Angina Pectoris

- Atherosclerosis of large coronary arteries
- Heart valve disease
- Thickening of heart muscles
- Coronary artery spasm
- Hypertension



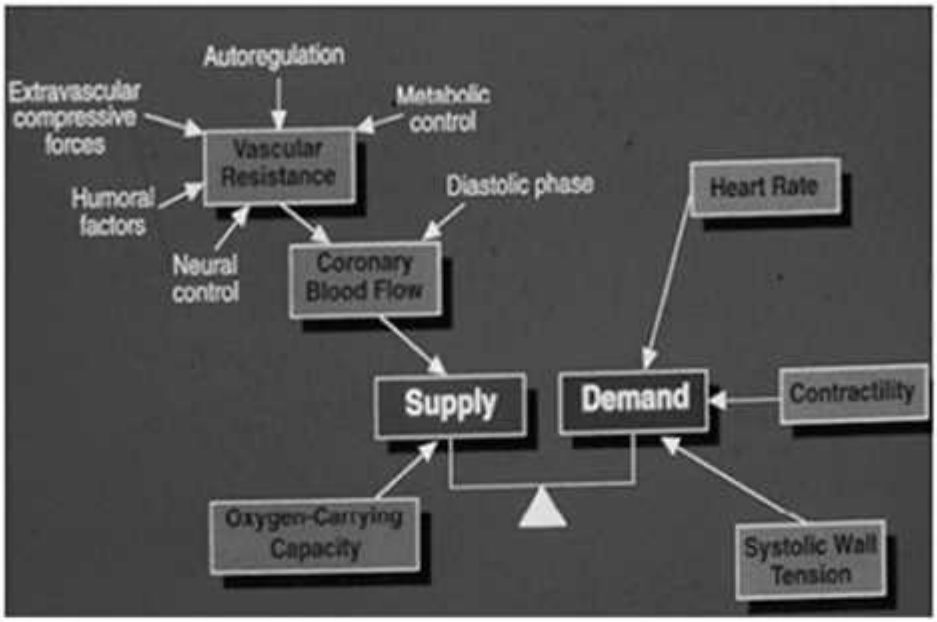
Symptoms of Angina Pectoris

- Gripping of central chest pain
- ↑ shortness of breath on exercise
- Sense of heaviness or numbness in the arm, shoulder, elbow or hand usually on the left side
- Constricting sensation in the throat
- Mild ache to severe pain
- Sweating and fear



Pathogenesis and types of Angina

- Imbalance between myocardial oxygen **demand and supply**



Stable/ Typical/ Exertional/ Classical Angina

- Provoked by physical exertion
- Heaviness, squeezing and sensation of constriction in the chest
- Pain subsides on resting
- Depression in ST segment of ECG
- No elevation in the blood enzyme level if no myocardial injury

Variant/ Prinzmetal Angina

- Pain at rest
- No relationship with physical activity
- Occur due to coronary artery spasm
- Spasm – due to release of vasoconstrictor by mast cells in coronary artery
- Attacks are painful, occur between midnight & daily morning
- ST segment elevation in ECG
- Patient respond well to vasodilator like nitroglycerine

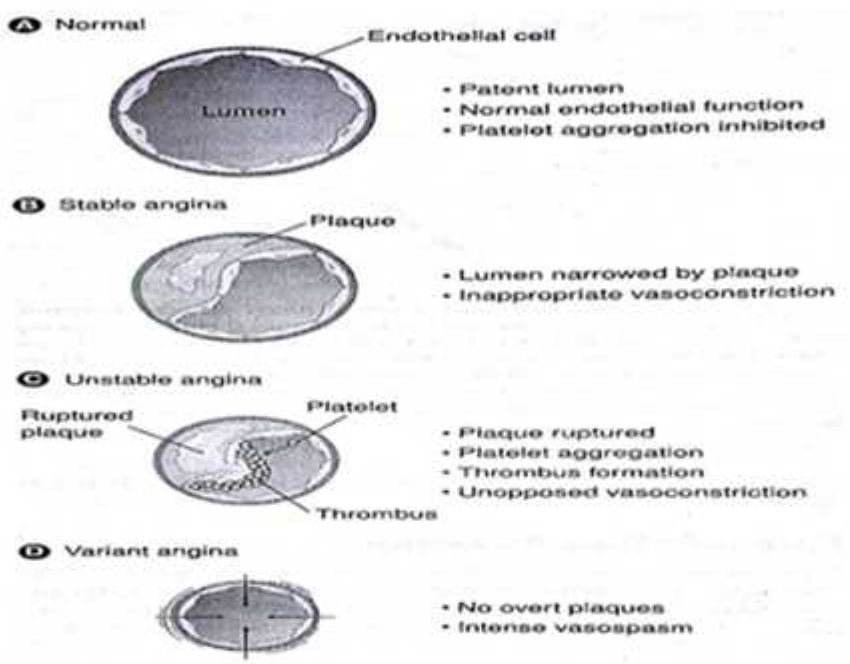
Unstable/ Atypical/ Cresendo/ Preinfarction Angina or Acute coronary insufficiency

- Frequent onset of pain for longer duration

- Occurs often at rest
- Indication of myocardial infarction

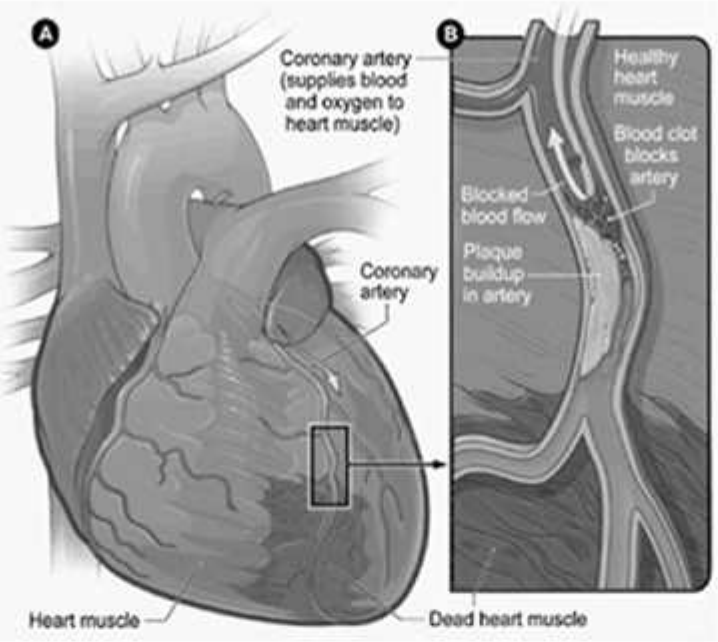
Microvascular angina

- Chest pain , no apparent coronary artery damage
- Poor functioning of blood vessels of heart, arm or legs
- May occur during exercise or at rest



Myocardial infarction

- Myocardial infarction / Heart attack results from complete obstruction to blood flow in coronary artery
- Imbalance in supply and demand of O_2 to myocardium
- Underlining cause – coronary artery disease



Symptoms of myocardial infarction

- Severe chest pain
- Sweating
- Chest pain radiating through jaw, shoulder, arms and back
- Epigastric discomfort with or without nausea/ vomiting
- Sproathy and blood stained sputum
- Dizziness, weakness, Anxiety
- Irregular heart beat
- Heart burn & indigestion

Etio-pathogenesis of Myocardial infarction

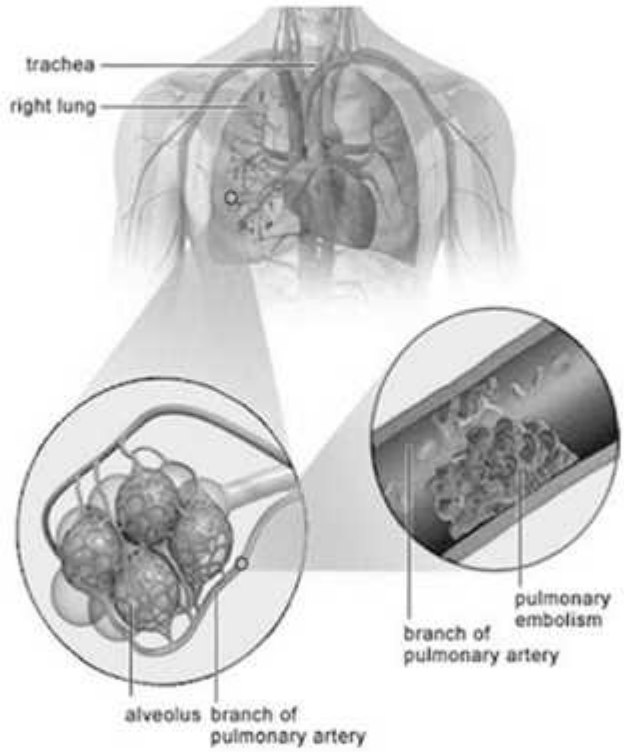
Atherosclerotic causes

- Accounts for 75% of cases
- Fatty streak deposits on the coronary artery
- Endothelium develop into an atherosclerotic plague depending on the presence of risk factors
- Risk factors – HT, DM, Smoking, Hyperlipidemia
- Plaque progression, proliferation and disruption of integrity of blood vessel

- Results in narrowing off coronary artery & MI

Non atherosclerotic causes

- Accounts for 10% of the causes of MI
- Coronary vasospasm
- Inflammation of arteries
- Coronary embolism
- Development of thrombosis
- Injury



Complications of Myocardial infarction

- Cardiac arrhythmia
- Congestive heart failure
- Cardiogenic shock
- Rapture of heart
- Mural thrombosis

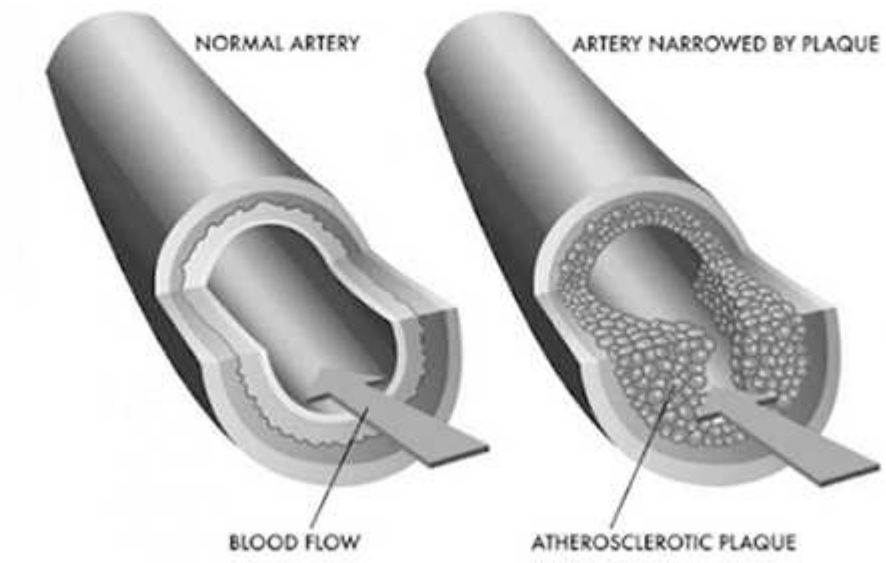
- Thromboembolism

Summary

- Angina is the discomfort due to transient myocardial ischemia where heart muscle does not receive enough blood (nutrient & O_2) resulting in chest pain
- Myocardial infarction / Heart attack results from complete obstruction to blood flow in coronary artery
- Causes of angina and MI include Atherosclerosis of large coronary arteries, heart valve disease, thickening of heart muscles, coronary artery spasm, hypertension
- Occurs mainly due to the imbalance in supply and demand of O_2 to myocardium

Atherosclerosis

- Atherosclerosis or atheroma
- Patchy focal disease of arterial wall
- Patchy thickening of the intimal layer of arterial wall
- Due to lipid deposition or fibrosis tissue formation



Major risk factors of Atherosclerosis

- Age
- Family history & genetics

- Racial risk – whites are at greater risk than blacks
- Excess lipid deposition
- Hypertension
- Smoking
- Diabetes mellitus

Minor risk factors of Atherosclerosis

- Obesity
- Lack of exercise
- Sedentary life style
- Use of oral contraceptives
- Alcohol consumption
- Stressful life
- Dietary factors
- Viral infection

Symptoms of Atherosclerosis

Symptoms vary depending on the organ involved

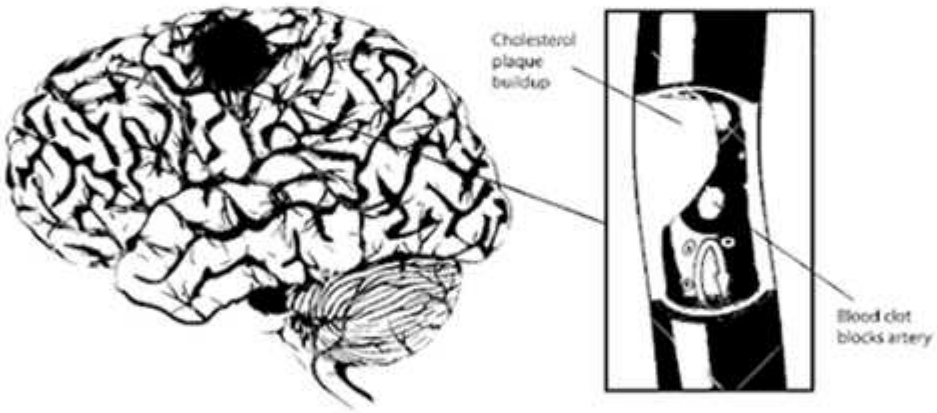
Heart

- Restricted blood supply to heart
- Angina & Myocardial infarction
- Shortness of breath
- Sweat

- Nausea
- Dizziness
- Palpitation

Brain

- Narrowing of arteries supplying brain
- Causes ischemic attacks
- Head ache
- Paralysis of one side of the body
- Numbness in various parts
- Visual disturbance
- Stroke

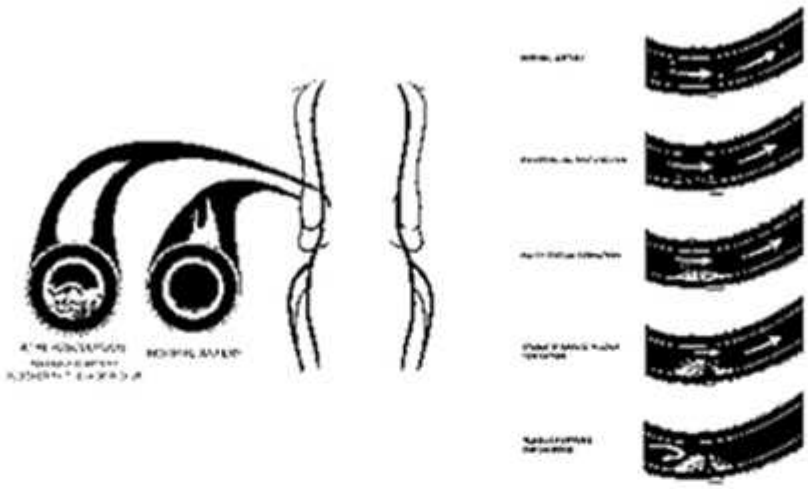


Abdomen

- Dull pain is felt in the abdomen
- Due to blockage of arteries supplying intestine
- Vomiting
- Diarrhoea
- Constipation

Leg

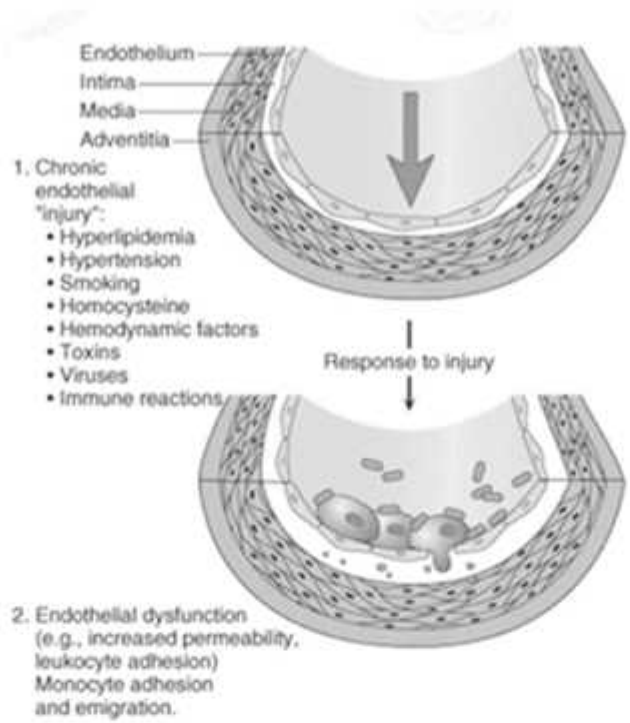
- Narrowing of artery supplying leg
- Pain in the leg
- Hair loss in leg



Pathogenesis of Atherosclerosis

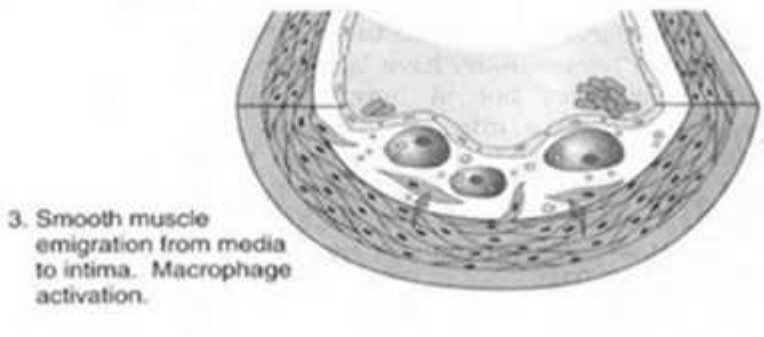
Endothelial injury

- Atherosclerosis is initiated by injury of endothelium
- In large & medium size arteries
- Causes include smoking
- Hypertension
- Chronic hyperlipidemia



Internal smooth muscle cell proliferation

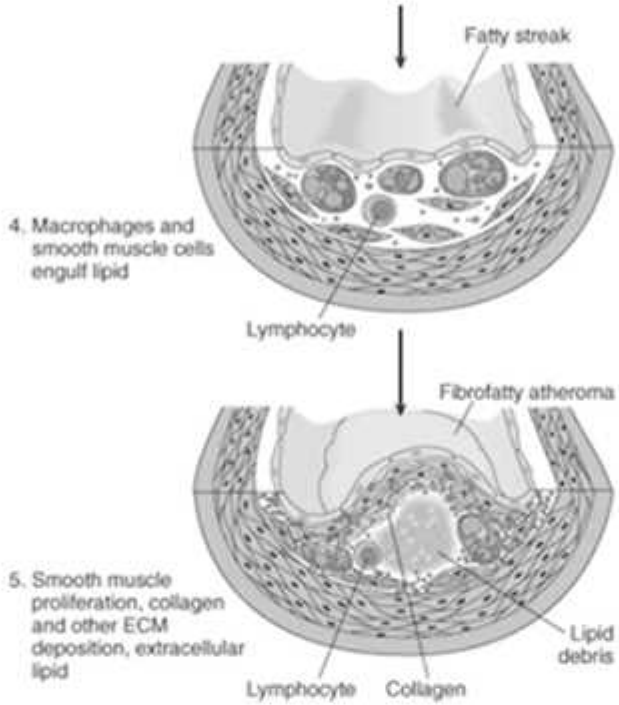
- Subsequent to endothelial injury
- Following disruption of endothelial layer
- Smooth muscle cell of blood vessels
- Cells of endothelium
- Proliferate under influence of – PGDF, EDGF, TGF β
- More synthesis of matrix protein



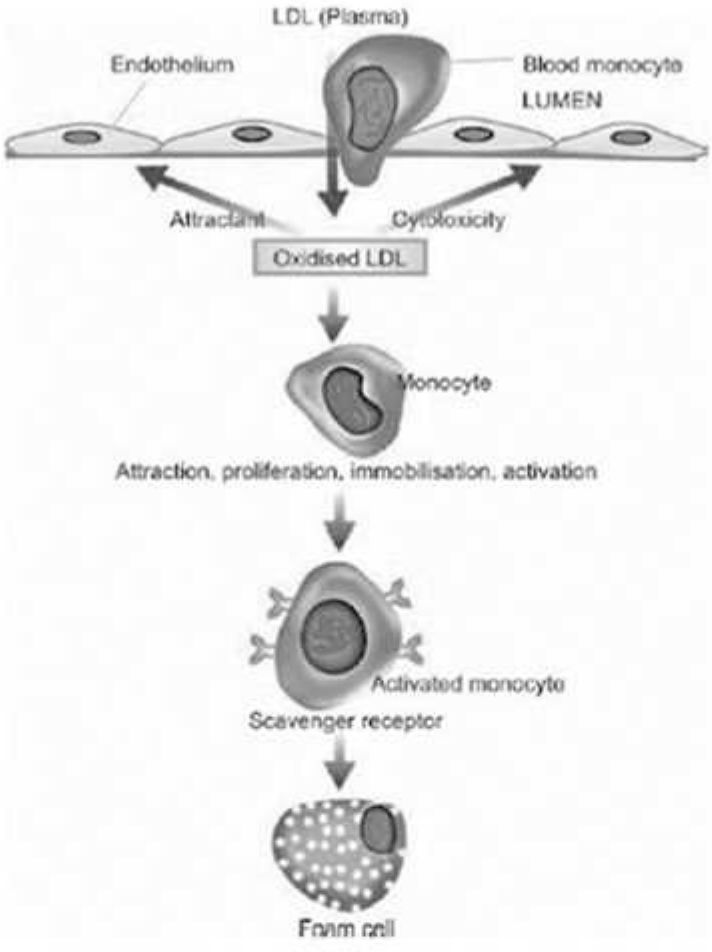
Lipoprotein entry into intima

- LDL from blood enters intima & get oxidized

- Oxidized LDL attracts monocytes
- Activates monocytes to macrophages
- Combination of oxidized LDL & macrophages - Lipid laden foam cells
- Major factor contributing to plaque formation



Mechanism involved in the formation of Foam cells



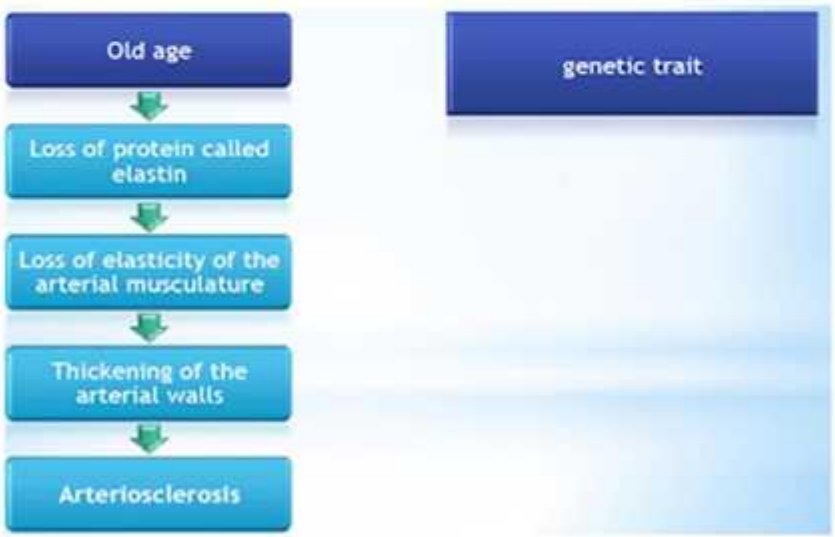
Summary

- Atherosclerosis or atheroma is a patchy focal disease of arterial wall
- Patchy thickening of the intimal layer of arterial wall due to lipid deposition or fibrosis tissue formation
- The main mechanism involved in the development of atheroma is endothelial injury
- Endothelial injury is followed by proliferation and formation of foam cells

ARTERIOSCLEROSIS

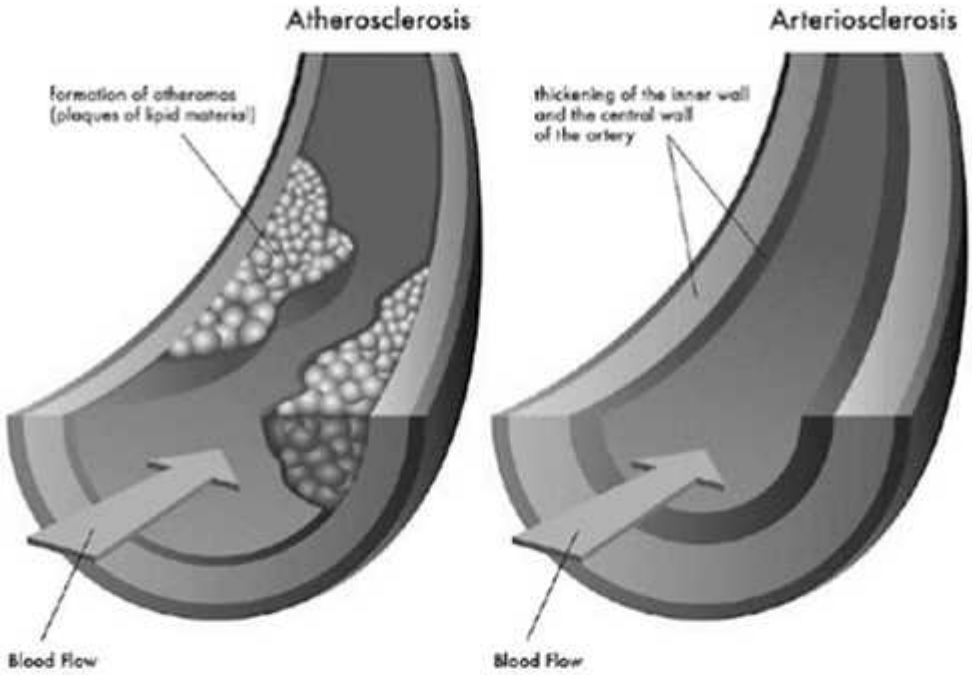
- Arteriosclerosis refers to the thickening and hardening of the medium or large arteries.
- Atherosclerosis is a form of arteriosclerosis in which cholesterol deposits line the inner wall of the artery.
- Arteriosclerotic plaque is a build-up of calcium on the inside of the artery walls. Both terms tend to be used interchangeably to describe the clogging and hardening of the arteries.
- Arteriosclerosis occurs either as a result of high blood pressure, high cholesterol or both.
- High blood pressure can cause the arteries to become stiff and thick, which restricts blood flow throughout the body.
- High cholesterol can cause an excessive build-up of plaque inside the arteries that significantly restrict blood flow.
- Arteriosclerosis most commonly occurs in the arteries of the heart, but it can affect any arteries within the body.

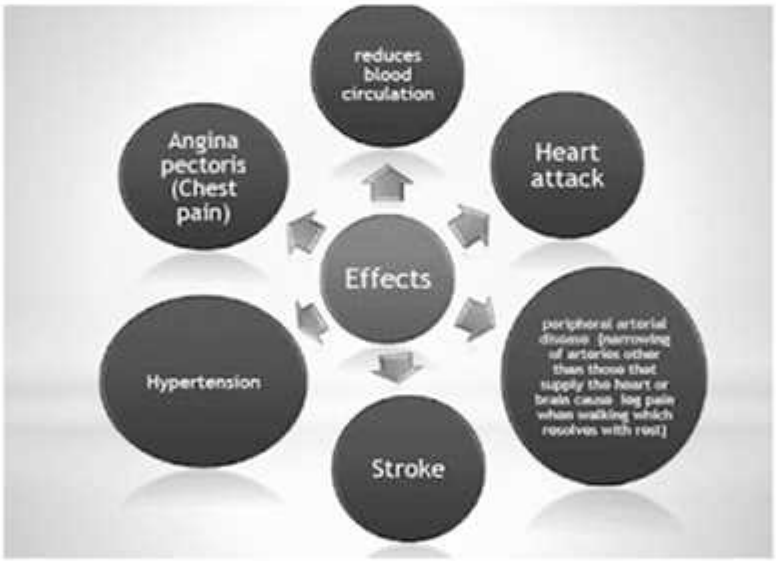
Factors that causes arteriosclerosis



Risk factors of Arteriosclerosis

- obesity
- smoking
- diabetes
- Inactivity
- diet high in saturated fat & low in healthy fruits, vegetables





Treatment of Arteriosclerosis

- **Lifestyle Modifications**-In the early stages of arteriosclerosis, lifestyle modifications include eating a diet low in cholesterol and salt.
- A healthy diet, along with getting regular exercise, might help slow and possibly even stop the progression of the disease.
- smokers should stop in order to prevent further artery damage.
- **Medications**-Medications, including those for blood pressure and high cholesterol, may be used to control conditions that have contributed to the development of arteriosclerosis.
- aspirin and anticoagulants

- **Bypass Surgery**-using a blood vessel from another part of the body or a synthetic tube to completely bypass the damaged artery.

Signs of Arteriosclerosis

- A decreased pulse in a narrowed artery
- Decreased blood pressure in a limb
- A bulge in the abdomen or behind the knee
- High blood pressure
- Kidney infection
- Shortness of breath
- Dizziness
- Neurological Symptom-Arteriosclerosis may affect the arteries that supply the brain.

Summary

- Arteriosclerosis refers to the thickening and hardening of the medium or large arteries
- artery walls become calcified or hardened which results in a loss of flexibility and elasticity
- Arteriosclerosis is a disease process that occurs gradually over time, and although the hardening of the heart's arteries receives most attention, arteriosclerosis can happen anywhere along the miles of these blood vessels in your body
- Avoid smoking as this can increase the risk of complications such as stroke and heart attack

RESPIRATORY SYSTEM

Asthma

- Disorder of the respiratory system that leads to episodic difficulty in breathing
- Chronic inflammatory disorder of the airways in which many cells and cellular elements play a role
- Mast Cells, Eosinophils, T Lymphocytes, Macrophages, Neutrophils , Epithelial Cells

Bronchial Asthma

- Also called reversible airway obstruction
- Clinical syndrome characterized by recurrent bouts of bronchospasm
- Increased responsiveness of the tracheobronchial smooth muscles to various stimuli
- Results in narrowing of the airway
- Chronic inflammatory disorder with reversible airflow obstruction
- Inflammation of bronchial wall mediated by eosinophils, mast cells & lymphocytes
- Hyper-responsiveness of bronchi – narrow readily with stimuli
- In late stages – irreversible

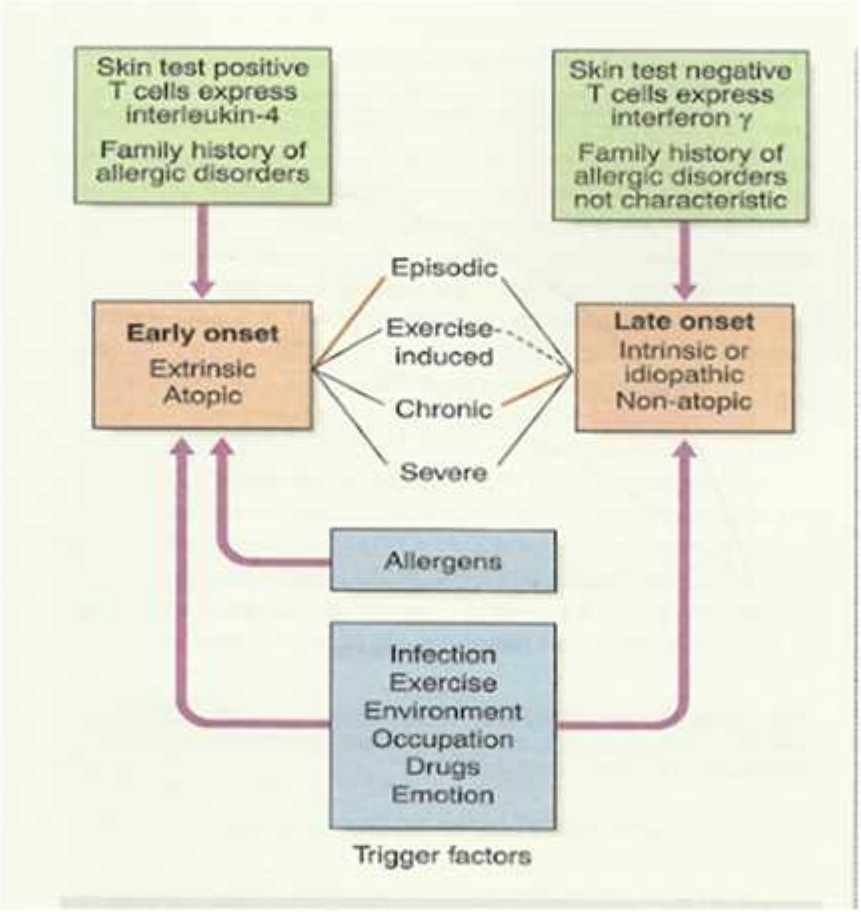
Etiology of Asthma

Extrinsic or allergic

- History of `atopy` in childhood
- Family history of allergies
- Positive skin test
- Raised IgE level
- Below 30 years of age
- Less prone to status asthmaticus

Intrinsic or idiosyncratic

- No family history of allergy
- Negative skin test
- No rise in IgE level
- Middle age onset
- Prone to status asthmaticus



Triggers

Drugs

Aspirin, ibuprofen and other prostaglandin synthetase inhibitors, beta blockers

Foods

Nuts, fish, sea food, dairy products, food colouring

Other industrial chemicals

Wood or grain dust, cotton dust, cigarette etc

Miscellaneous

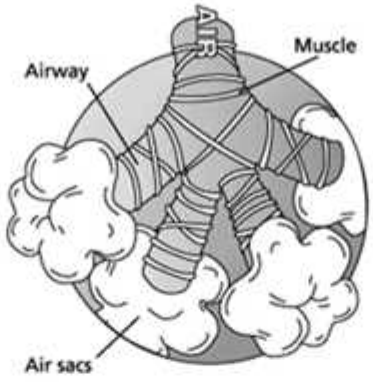
Cold, exercise, hyperventilation ,viral respiratory tract infections, emotion or stress

Pathophysiology of Asthma

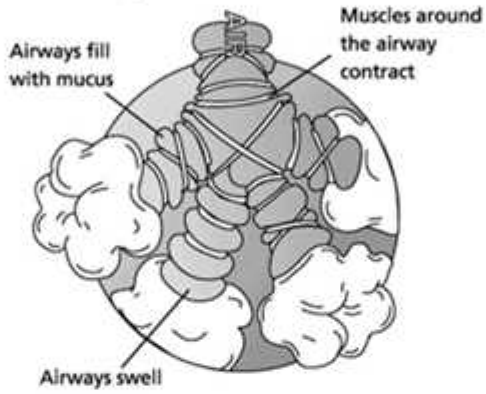
Main features of asthma:

- Hypertrophy of bronchial smooth muscle
- Hyperplasia of epithelial cells
- Mucus gland hypertrophy
- Airway oedema
- Acute bronchoconstriction
- Impaired mucociliary clearance

Before an Asthma Episode



After an Asthma Episode



- Early exposure to
  - Allergens
  - Viral infections
  - Diet induced
- Early onset: Atopic
  - Positive family history
  - Readily form IgE to common allergens react with mast cells on surface & activate IgE – histamine release
  - Many more mediators

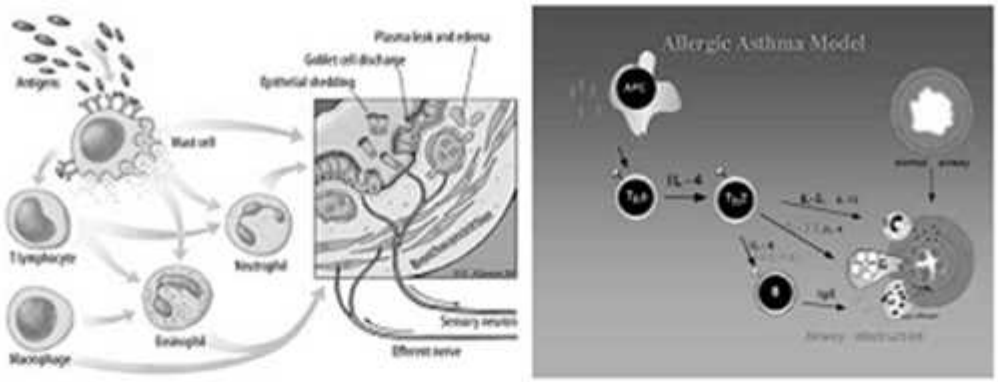
 Changes in the airway

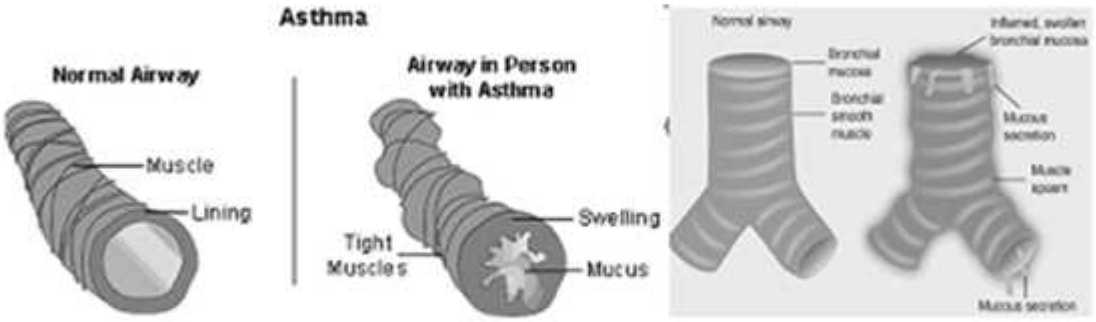
  Epithelial shedding

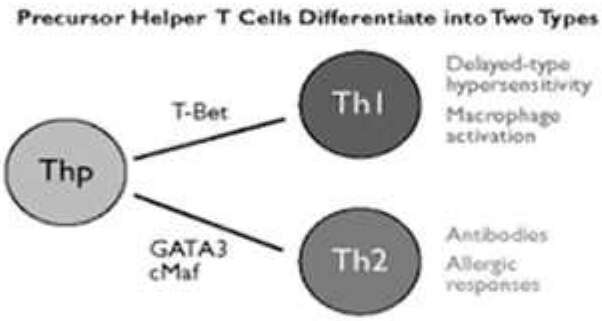
  Airway hyper-responsiveness

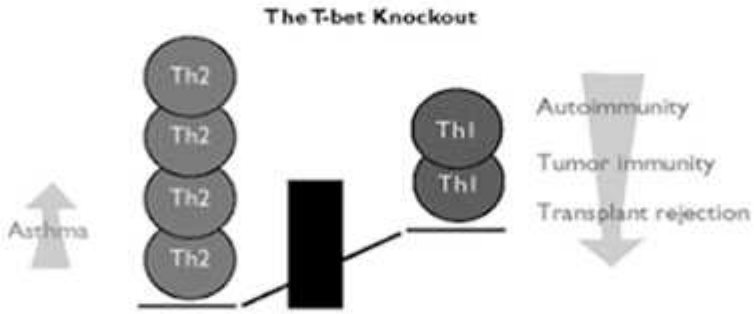
- Microvascular leakage – exudate mucus plugging
- Neuronal imbalance – bronchoconstriction

- IgE-antibody-mediated reaction on the surface of the mast cell leads to release of mast cell components
- Histamine - triggers rapid bronchoconstriction
- Eosinophils release LTC4 and PAF
- Epithelial damage and thick viscous mucus produced causing deterioration in lung function
- Epithelial damage
- Increases access of various irritants to the cholinergic receptors,
- Bronchoconstriction mediated by the parasympathetic nervous system









Signs and Symptoms of Asthma

- Persistent cough
- Dyspnoea - difficulty in breathing
- Wheezing - a high pitched noise due to turbulent airflow through a narrowed airway
- Tightness of chest

- Shortness of breath
- During attacks - fatigue, cyanosed, lethargic, confused, breathless, rapid breathing (> 30 breaths/minute)

Clinical Features of Asthma

- Episodic or chronic
- Triad of:

  - Dyspnea (difficulty in breathing)

  - Wheezing (additional sounds)

  - Cough (persistent)
- Productive sputum
- Others

  Tachycardia

  Pulsus paradoxus

  Sweating

  Cyanosis, bradycardia in severe cases

  Silent chest

SUMMARY

- Chronic inflammatory disorder with reversible airflow obstruction
- Inflammation of bronchial wall mediated by eosinophils, mast cells & lymphocytes
- IgE-antibody-mediated reaction
- Release of mast cell components which triggers rapid bronchoconstriction
- Persistent cough, recurrent episodes of difficulty in breathing associates with wheezing, chest tightness, shortness of breath, abnormal lung function are the common symptoms

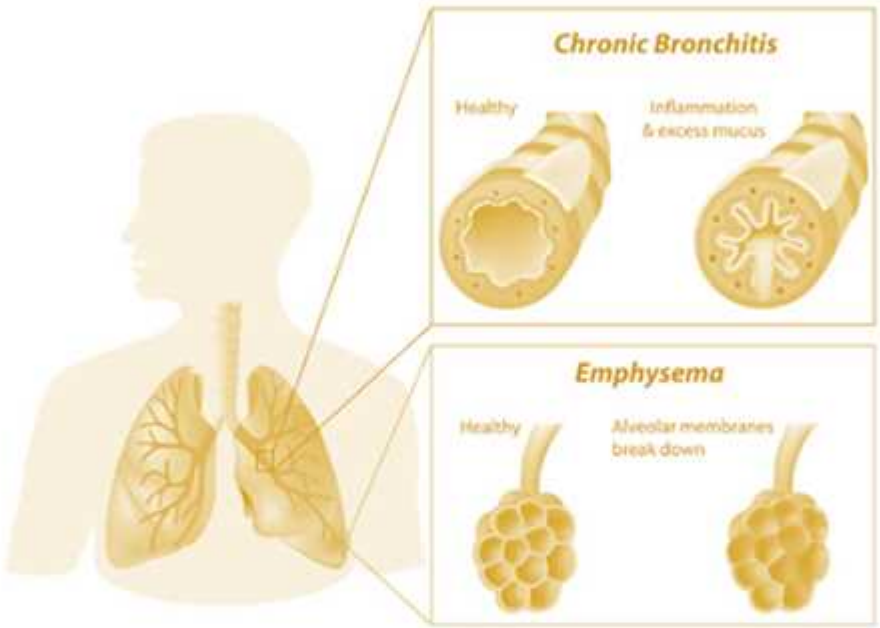
Chronic Obstructive Pulmonary Disease (COPD)

"A chronic slowly progressing disorder characterized by air flow obstruction leading to reduced pulmonary inspiratory & expiratory capacity"

- Disease may co-exist with asthma

Two major forms of COPD

- Chronic bronchitis
- Emphysema



Chronic bronchitis

- Characterized by excessive mucus production by the tracheo-bronchial followed by edema & bronchial inflammation leading to airway obstruction
- It is associated with cigarette smoking & air pollution

Pathogenesis of chronic bronchitis

Two pathological processes underlining the development of chronic bronchitis include

1. Hypersecretory disorder

- Characterized by expectoration with increased susceptibility to respiratory infections
- Normally, cilia & mucus in the bronchi protect against inhaled irritants which are trapped and expectorated

- Persistent irritation causes proliferation of mucus secreting glands & goblet cells in the bronchial epithelium leading to hypersecretion of thick & viscous mucus

- Accumulation of mucus inturn causes inflammation and recurrent viral & bacterial infections

2. Chronic inflammation & edema causes thickening of bronchio & alveolar walls

- Alveoli gets distorted, affects blood vessels closely associated with them, leading to vasoconstriction and pulmonary hypertension

- Reduction of gas exchange across alveolar epithelium – hypoxemia

- Sustained pulmonary hypertension – increased right ventricular pressure within heart, right ventricular hypertrophy and failure

- Pulmonary edema results followed by activation of renin angiotensin, aldosterone system, salt & water retention – reduction in renal blood flow

Emphysema

- Condition of permanent destructive enlargement of respiratory bronchioles, alveolar ducts & alveolar sac

- Adjacent alveoli becomes indistinguishable from one another

2 main consequence of emphysema

- Loss of available gas space & impaired gas exchange

- Loss of elastic recoil in the small airways leading them to collapse during expiration

Pathogenesis of emphysema

Arise as a consequence of 2 critical imbalances

1. Protease – antiprotease imbalance
2. Oxidant – antioxidant imbalance

Protease – anti protease theory

- Emphysema results from gradual progressive loss of elastic tissue in lungs due to an imbalance between proteolytic enzymes & protective factors

- Macrophages & neutrophills releases lysosomal enzymes (elastase) – capable of destroying connective tissue in the lungs

- Normal condition – protective mechanism called α_1 – anti trypsin or α_1 – protease inhibitor inhibits proteolytic enzyme and prevent damage

- α_1 – anti trypsin is present in serum, tissue fluids & macrophages
- Deficiency of α_1 – anti trypsin causes destruction of elastic tissue leading to emphysema

Oxidant – antioxidant imbalance

- Normally lungs contains anti oxidants like SOD, glutathione - reduces oxidative damage
- Tobacco smoke, activated neutrophills – increases oxygen free radicals – depletes antioxidant mechanism – tissue damage
- Inactivation of antiproteases, functional deficiency without enzyme deficiency

Symptoms of COPD

- Chronic cough (after 20 or > cigarettes/day)
- Dyspnea (during physical activity and rest)
- Frequent respiratory infections
- Production of purulent sputum
- Bluish discoloration of lips and nail beds
- Morning headaches
- Wheezing
- Weight loss
- Pulmonary hypertension
- Peripheral oedema

- Hemoptysis

Summary

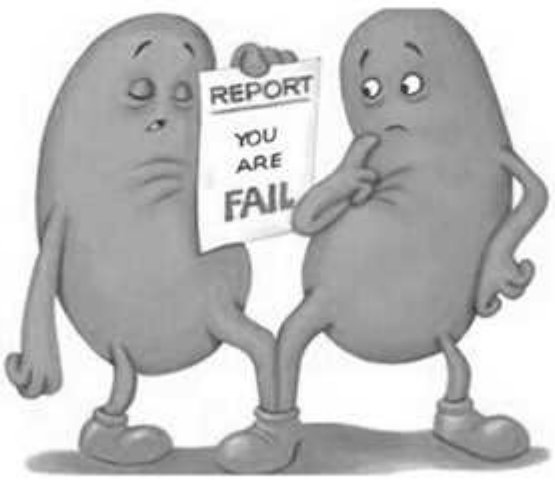
- COPD is the most prevalent manifestation of obstructive lung disease, mainly comprises chronic bronchitis and emphysema
- Reduction of overall personal exposure to tobacco smoke, occupational dusts, chemicals and pollutants is an important goal to prevent the onset and progression of COPD
- Risk factors for COPD include host factors (a, -antitrypsin deficiency and airway hyperresponsiveness) and exposures (tobacco smoke, occupational dusts and chemicals, indoor and outdoor pollutants, infections) and socio-economic status

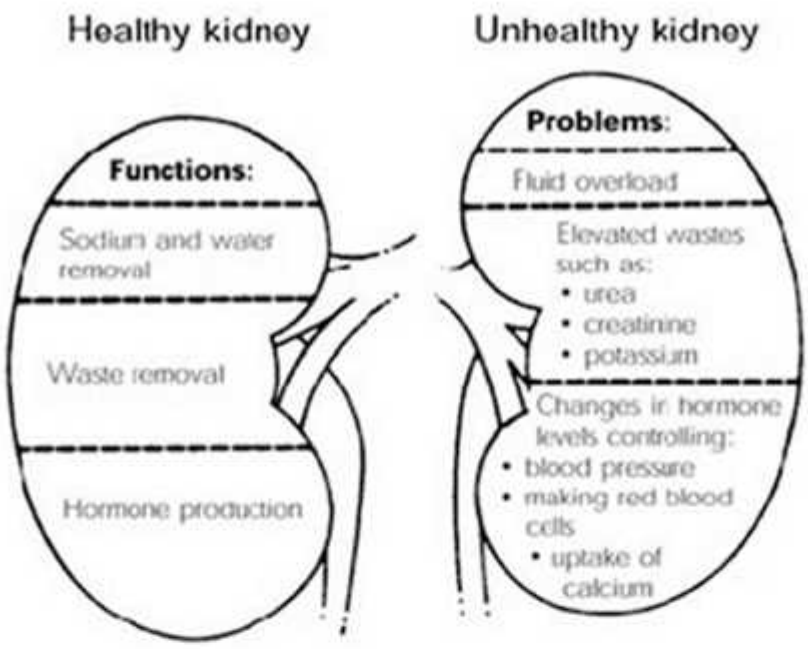
Renal Failure

- Cessation of glomerular filtration as kidney fails to function normally
- Leads to accumulation of Urea, creatinine

Two type of Renal failure

- **Acute renal failure**
- **Chronic renal failure**





Acute renal Failure

- Kidney stops functioning all of a sudden

Categorized by

- Oliguria
- Anuria
- Accumulation of metabolites

Etiology of acute renal Failure

Pre renal cause

- Causes above the level of kidney
- Reduction in blood volume
- Renal ischemia

Intra renal causes

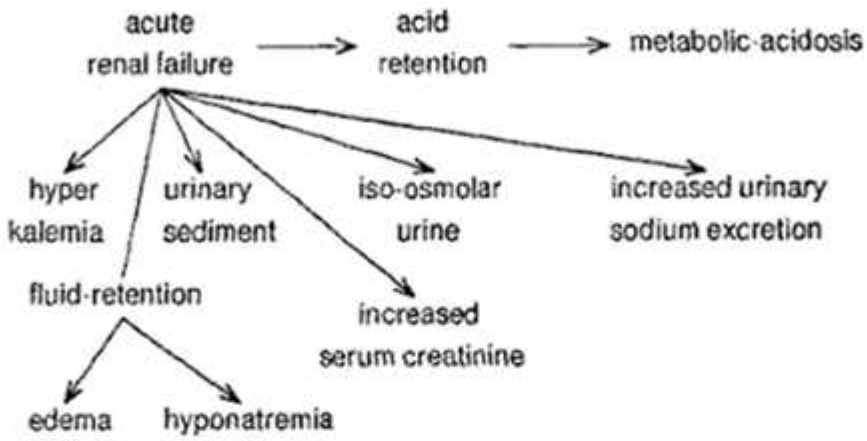
- Glomerular disease
- Disease of renal tubules
- Pyelonephritis

Post renal causes

- Obstruction of urine flow

Other causes – kidney stones drugs

Manifestations of acute renal failure



Chronic renal failure

- Progressive & irreversible damage in GFR
- Slow destruction of renal tubule
- Leads to death

Etiology of Chronic renal failure

- Chronic glemerulo nephritis
- Diabetic nephropathy
- Polycystic kidney disease
- Exprosure to nephrotxins

Clinical Manifestations of Chronic renal failure

Renal manifestation

- Metabolic acidosis
- Hyperkalaemia
- Sodium & water retention

- Azotemia

Extra renal manifestation

- Anaemia
- Ureamic frost
- Pulmonary congestion
- Azotemia
- Osteomalacia

Pathogenesis of Chronic renal failure

Mild CRF

- Decreased renal reserve
- GFR 50% of normal filtration
- Renal parenchyma is marginally lost
- Patient asymptomatic\

Moderate CRF (Renal insufficiency)

- 75% of renal parenchyma gets destroyed
- GFR 25% of normal value

Severe chronic renal failure

- 90% renal parenchyma damage
- GFR 10% of normal values
- Tubular cells non functional
- Imbalance in sodium & water retention

Final stage of kidney

- Renal parenchyma completed destroyed
- GFR 5% of normal value
- Complete accumualtion of waste products
- Require dialysis therapy

Summary

- Renal failure is the cessation of glomerular filtration as kidney fails to function normally
- It Leads to accumulation of Urea, creatinine
- Renal failure is of two kinds - Acute and chronic renal failure
- In ARF, kidney stops functioning all of a sudden and is categorized by oliguria, anuria, accumulation of metabolites
- CRF is characterized by Progressive & irreversible damage in GFR , slow destruction of renal tubule, leading to death

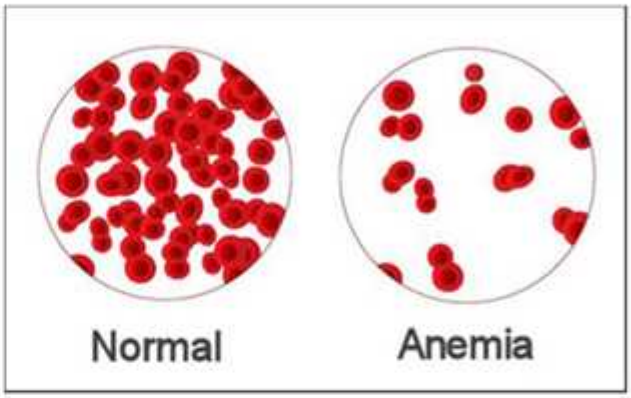
UNIT III

Haematological diseases

BLOOD

- Components of Blood

Plasma	Cells
Water (97%)	Red blood cells
Ions	White blood cells
Organics	Platelets
Protein	
Sugars	
Amino acids	
Lipids	
Trace elements	
Dissolved gases	



Anemia

- Condition in which the oxygen-carrying capacity of blood is reduced
- Characterized by reduced numbers of RBCs or a decreased amount of hemoglobin in the blood

General manifestations of anemia

Reduced oxygen delivery can result in the following:

• Ischemia

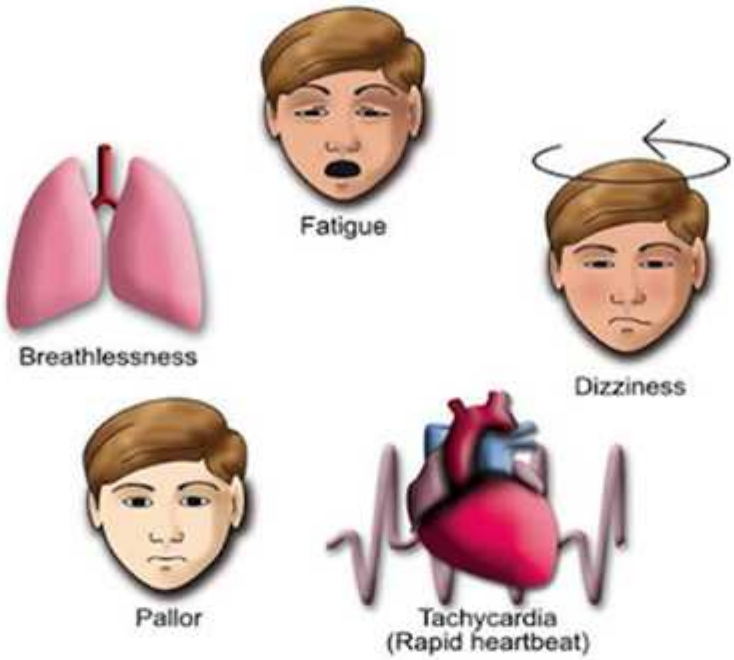
• Fatigability

• Breathlessness upon exertion

• Exercise intolerance

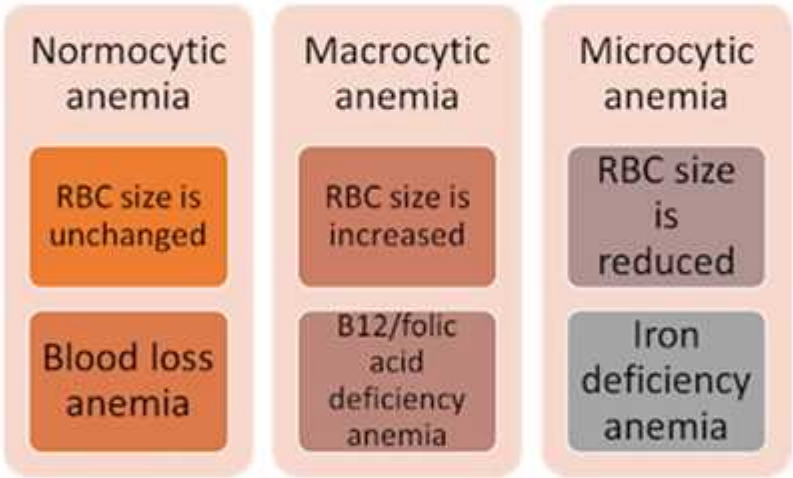
• Pallor

• Increased susceptibility to infection



Classification of Anemia

1) Based on Size changes



2) Color changes (due to altered hemoglobin content)

- **Normochromic —** Normal hemoglobin concentration
- **Hypochromic —** Reduced hemoglobin concentration

Example: Iron deficiency anemia may be classified as a microcytic, hypochromic anemia as both red blood cell size and hemoglobin content are reduced

3) Blood loss anemia: Anemia that results from acute blood loss.

4) Iron-deficiency anemia: It can occur as a result of iron-deficient diets

5) Cobalamin-deficiency or folate-deficiency anemia

6) Inherited anemia- Sickle cell anaemia

Iron Deficiency Anemia

- The commonest nutritional deficiency disorder present throughout the world is iron deficiency

Absorption

- **Haem iron** is better in absorption than non haem iron
- **Non-haem iron** is released as ferrous or ferric form
- Transport across the membrane by divalent metal transporter 1 (DMT 1)

TRANSPORT:

- Iron is transported in plasma bound to a β-globulin, *transferrin*, synthesised in the liver
- Transferrin bound iron utilise for haemoglobin synthesis.
- Transferrin is reutilised after iron is released from it.

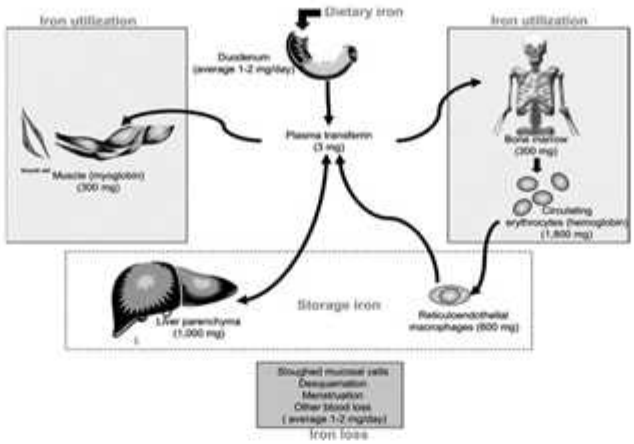
EXCRETION:

The body is unable to regulate its iron content by excretion alone. The amount of iron lost per day is 0.5-1 mg.

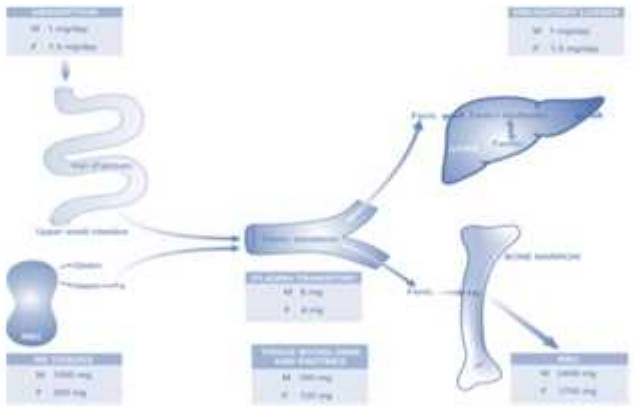
DISTRIBUTION. In an adult, iron is distributed in the body as under:

- **1. Haemoglobin**—(65%).
- **2. Myoglobin**—(3.5%).
- **3. Haem and non-haem enzymes**—(0.5%).
- **4. Transferrin-bound iron**—(0.5%)
- **5. Ferritin and haemosiderin**—a (30%).

Iron absorption



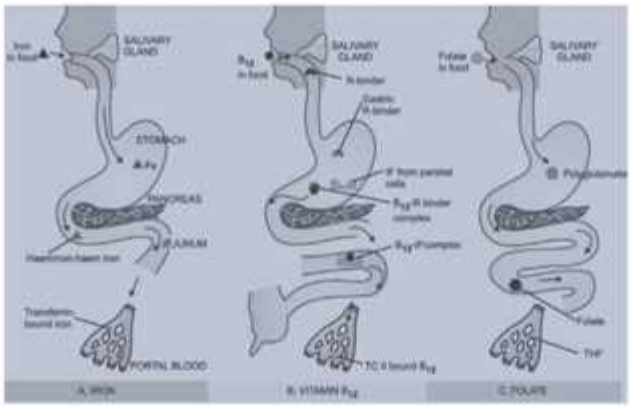
Absorption of Iron



Pathogenesis of Iron deficiency anaemia

- Iron deficiency anaemia develops when the supply of iron is inadequate for the requirement of haemoglobin synthesis.
- The development of iron deficiency depends upon one or more of the following factors:

1. Increased blood loss
2. Increased requirements
3. Inadequate dietary intake
4. Decreased intestinal absorption



Etiology of Iron deficiency anaemia

I. INCREASED BLOOD LOSS

1. *Uterine* e.g. excessive menstruation in reproductive years, repeated miscarriages, at onset of menarche, post-menopausal

uterine bleeding

2. *Gastrointestinal* e.g. peptic ulcer, haemorrhoids, hookworm infestation, cancer of stomach and large bowel, oesophageal varices, hiatus hernia, chronic aspirin ingestion, ulcerative colitis, diverticulosis

3. *Renal tract* e.g. haematuria, haemoglobinuria

4. *Nose* e.g. repeated epistaxis

5. *Lungs* e.g. haemoptysis

II. INCREASED REQUIREMENTS

1. Spurts of growth in infancy, childhood and adolescence

2. Prematurity

3. Pregnancy and lactation

III. INADEQUATE DIETARY INTAKE

1. Poor economic status

2. Anorexia e.g. in pregnancy

3. Elderly individuals due to poor dentition, apathy and financial constraints

IV. **DECREASED ABSORPTION**

1. Partial or total gastrectomy

2. Achlorhydria

3. Intestinal malabsorption such as in coeliac disease

Clinical Features of Iron deficiency anaemia

- Iron deficiency anaemia is much more common in women between the age of 20 and 45 years than in men
- More frequent in premature infants.

Clinical consequences of iron deficiency:

1)anemia

2)epithelial tissue changes

Treatment of Iron deficiency anaemia

The management of iron deficiency anaemia consists of 2 essential principles:

1) Correction of disorder causing the anaemia: checkup and investigations.
2) 2)Correction of iron deficiency: **i) Oral therapy**

ii) Parenteral therapy

Summary

- Anaemia is the condition in which the oxygen-carrying capacity of blood is reduced
- Characterized by reduced numbers of RBCs or a decreased amount of hemoglobin in the blood
- The commonest nutritional deficiency disorder present throughout the world is iron deficiency
- Iron deficiency anaemia develops when the supply of iron is inadequate for the requirement of haemoglobin synthesis

Megaloblastic Anaemia

- It is caused by impaired DNA synthesis and others by folate and vitamin B12 deficiency
- Abnormality in the haematopoietic precursors in the bone marrow - maturation of the nucleus is delayed relative to that of the cytoplasm.
- Formation of morphologically abnormal nucleated red cell precursor called megaloblast in the bone marrow

- Anaemia described is hyperchromic macrocytic

Etiological Classification of Megaloblastic Anaemia

I. VITAMIN B12 DEFICIENCY

A. **Inadequate dietary intake** e.g. strict vegetarians, breast-fed infants.

B. Malabsorption

1. Gastric causes: pernicious anaemia, gastrectomy, congenital lack of intrinsic factor.

2. Intestinal causes: tropical sprue, ileal resection, Crohn's disease, intestinal blind loop syndrome, fish-tapeworm infestation.

II. FOLATE DEFICIENCY

A. **Inadequate dietary intake** e.g. in alcoholics, teenagers, infants, old age, poverty.

B. Malabsorption e.g. in tropical sprue, coeliac disease, partial gastrectomy, jejunal resection, Crohn's disease.

C. Excess demand

- 1. Physiological: pregnancy, lactation, infancy.
- 2. Pathological: malignancy, increased haematopoiesis, chronic exfoliative skin disorders, tuberculosis, and rheumatoid arthritis.

D. Excess urinary folate loss e.g. in active liver disease, congestive heart failure

Pathophysiology of Megaloblastic Anaemia

- The common feature in megaloblastosis is a defect in DNA synthesis in rapidly dividing cells.
- RNA and protein synthesis are impaired.
- Unbalanced cell growth and impaired cell division occur since nuclear maturation is arrested.
- More mature RBC precursors are destroyed in the bone marrow prior to entering the blood stream (intramedullary hemolysis)

Vitamin B12

- Vitamin B12 or cobalamin is a complex organometallic compound having a cobalt atom situated within a corrin ring.
- The liver is the principal storage site of vitamin B12

- Major source of loss is via bile and shedding of intestinal epithelial cells.
- A major part of the excreted vitamin B12 is reabsorbed in the ileum by the IF resulting in enterohepatic circulation

Sources of Vitamin B12

- Micro-organisms (Soil, water animal intestine)
- Man and animals intestinal lumen but not absorbed 3-5 µg excreted daily in faeces
- Non veg foods: Muscle, liver, kidney, oysters,fish, egg yolk

Vegetable source: is pulses (legumes)

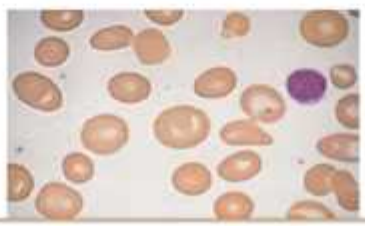
- Dairy milk in smaller amounts

- Daily requirement: 1-3 µg,
- Pregnancy & lactation 3-5 µg
- Commercial source: Streptomyces Griseus

Functions of B12

Vitamin B12 plays an important role in general cell metabolism

- Essential for normal haematopoiesis and for maintenance of integrity of the nervous system.
- Vitamin B12 acts as a co-enzyme



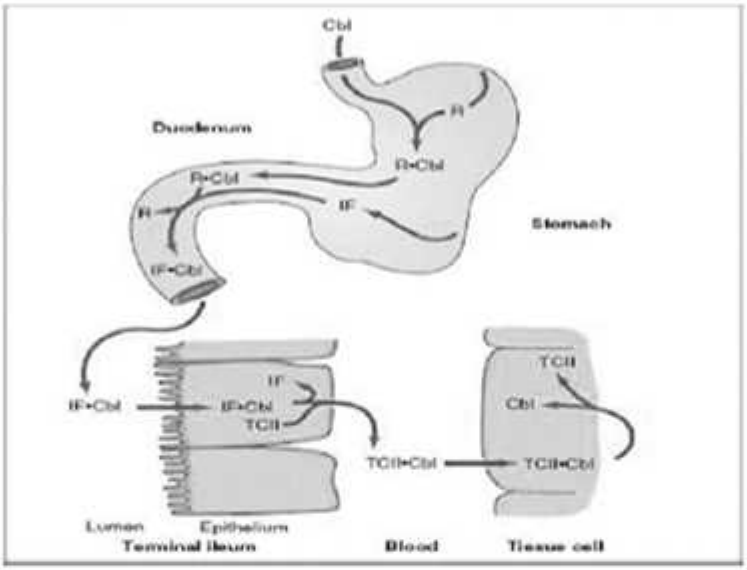
Pharmacokinetics of B12

Absorption:

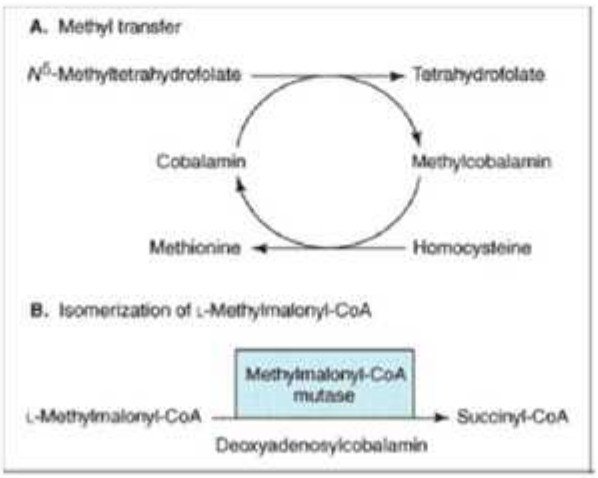
- Cobalamins in food are in bound form inactive, released by cooking (heat) and by proteolysis in stomach & intestine.

- Vit B12 is not soluble so absorption depends on various transfer factors

  - R- Factor, Intrinsic factor & Transcobolamin II



Metabolic functions of Vit B12



C: Purine biosynthesis reduced , defective DNA

- Methyl THF trapping & lack of S- adenosyl methionine can cause this

D: Cell growth & multiplication (Poultry)

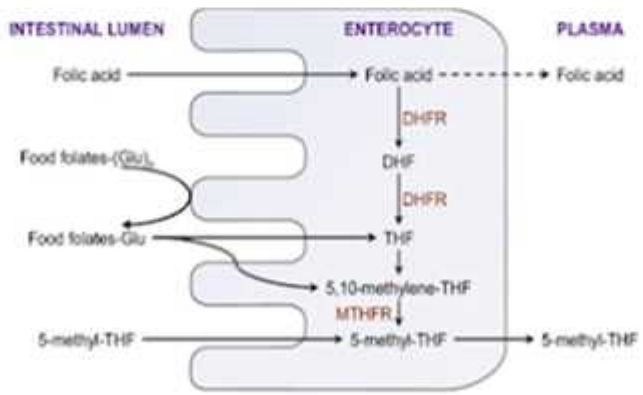
E: Role in folate uptake & storage

B12 Deficiency Symptoms

- Atrophic glossitis (shiny tongue)
- Shuffling broad gait
- Anemia and related sx
- Vaginal atrophy
- Malabsorption
- Jaundice
- Personality changes
- Hyperhomocysteinemia
- Neurologic symptoms (next slide)
- Copper deficiency can cause similar neurologic symptoms

Folate Metabolism

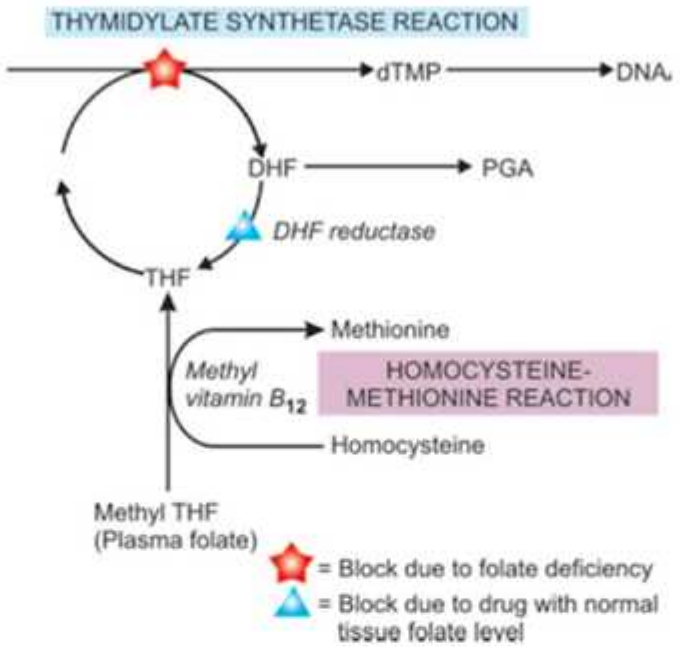
- **BIOCHEMISTRY:** Folate or folic acid, a yellow compound, is a member of water-soluble B complex vitamins -*pteroyl glutamic acid*
- **ABSORBTION:** from the duodenum and upper jejunum



- **TISSUE STORES.** The liver and red cells are the main storage sites of folate, largely as methyl THF polyglutamate form
- Total folate in body = 5 to 10 mg (1/3 in liver as methyl folate)

- **FUNCTIONS:** acts as a co-enzyme for 2 important biochemical reactions

1. Thymidylate synthetase reaction. Formation of deoxy thymidylate monophosphate (dTMP) from its precursor form, deoxy uridylate monophosphate (dUMP).
2. Methylation of homocysteine to methionine. This reaction is linked to vitamin B12 metabolism



Causes of Folate Deficiency

- Malnutrition: Destroyed by heat during cooking
- Alcoholism (decreased in 2-4 days): impairs enterohepatic cycle and inhibits absorption
- Increased requirement in hemolytic anemia, pregnancy, exfoliative skin disease
- IBD, celiac sprue
- Drugs
  - Trimethoprim, Methotrexate, Primethamine (inhib DHFR)
  - Phenytoin: blocks FA absorption, increases utilization (mech unknown)

Folate deficiency symptoms

- Similar symptoms as B12 save for neurologic symptoms
- Presentation is different classically:
  - Alcoholic
  - Very poor dietary intake

- Older
- Depressed
- Living alone

Treatment

- Hydroxycobalamin as intramuscular injection 1000 µg for 3 weeks and oral folic acid 5 mg tablets daily for 4 months.
- Rule out B12 deficiency prior to treament as folic acid will not prevent progression of neurologic manifestations of B12 deficiency

Sickle Cell Anaemia

- Sickle-cell disease (SCD), or sickle-cell anaemia or drepanocytosis, is an autosomal co-dominant genetic blood disorder characterized by red blood cell that assume an abnormal, rigid, sickle shape.

Haemoglobinopathies: Haemoglobin in RBCs may be abnormally synthesised due to inherited defects. These disorders may be of two types:

- *Qualitative disorders* e.g. sickle cell syndrome, other haemoglobinopathies.
- *Quantitative disorders* e.g. thalassaemias.

Sickle syndromes occur in 3 different forms:

- 1. *As heterozygous state* for HbS: sickle cell trait (AS).
- 2. *As homozygous state* for HbS: sickle cell anaemia (SS).
- 3. *As double heterozygous states* e.g. sickle β-thalassaemia, sickle-C disease (SC), sickle-D disease (SD).
- Sickle cell anaemia (SS) is a homozygous state of HbS in the red cells in which an abnormal gene is inherited from each parent.
- Red blood cells typically live 90–120 days, but sickle cells only survive 10–20 days

Pathogenesis of Sickle cell anaemia

1. Basic molecular lesion: *single point mutation* in one amino acid out — there is *substitution of valine for glutamic acid –*

- 6-residue position of the β-globin, producing Hb α2β2s2.

2. Mechanism of sickling: During deoxygenation, the red cells containing HbS change from biconcave disc shape to an elongated crescent-shaped or sickle-shaped cell- *sickling*

- Form elongated rod-like polymers
- Which align and distort the red cell into classic sickle shape

3. Reversible-irreversible sickling

4. Factors determining rate of sickling:

- i) Presence of non-HbS haemoglobins
- ii) Intracellular concentration of HbS.
- iii) Total haemoglobin concentration.
- iv) Extent of deoxygenation.
- v) Acidosis and dehydration.
- vi) Increased concentration of 2, 3-BPG in the red cells.

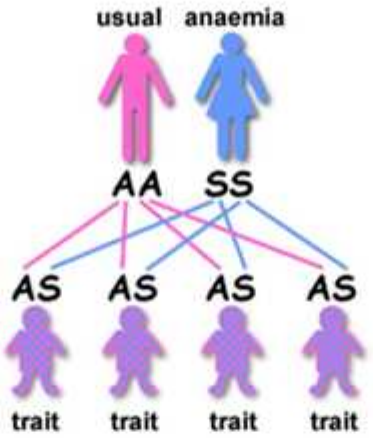
Sickle Cell Anemia vs. Sickle Cell Trait

- People who have sickle cell anemia are born with it; means inherited, lifelong condition.
- They inherit two copies of sickle cell gene, one from each parent.
- Sickle cell trait is different from sickle cell anemia. People with sickle cell trait don't have the condition, but they have one of the genes that cause the condition.
- People with sickle cell anemia and sickle cell trait can pass the gene on when they have children.

Inheritance of Sickle Cell Anemia

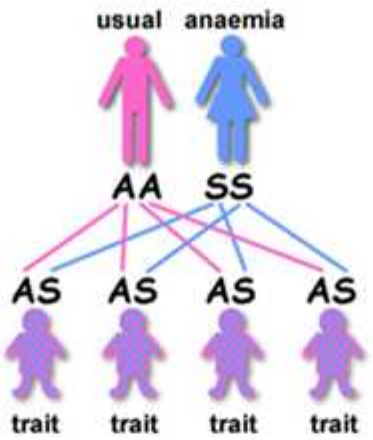
- If **one parent has sickle cell anaemia (HbSS) and the other is completely unaffected (HbAA)** then all the children will have sickle cell trait.
- None will have sickle cell anemia.
- The parent who has sickle cell anemia (HbSS) can only pass the sickle hemoglobin gene to each of their children.
- If both parents have sickle cell trait (HbAS) there is a one in four (25%) chance that any given child could be born with sickle cell anemia.
- There is also a one in four chance that any given child could be completely unaffected.

- There is a one in two (50%) chance that any given child will get the sickle cell trait.



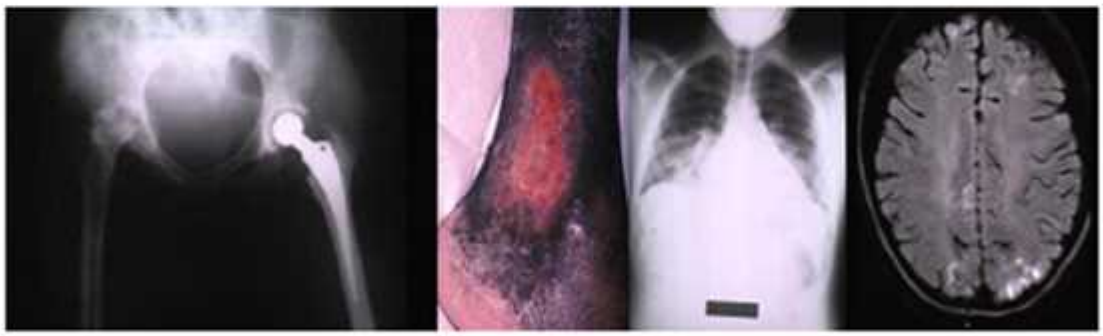
Clinical Features of Sickle Cell Anemia

- Painful episodes
- Pneumococcal disease
- Acute chest syndrome
- Splenic infarction
- Splenic sequestration
- Stroke
- Osteonecrosis
- Priapism
- Retinopathy
- Leg ulcers
- Gallstones
- Renal abnormalities
- Osteopenia
- Nutritional deficiencies
- Placental insufficiency
- Pulmonary hypertension

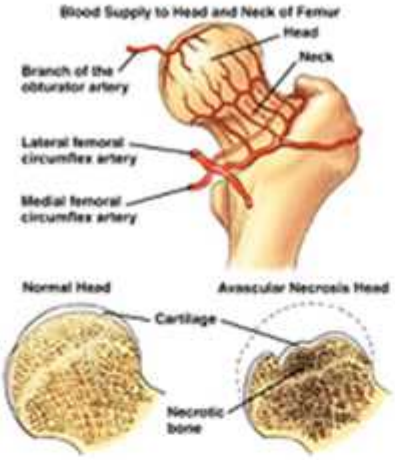


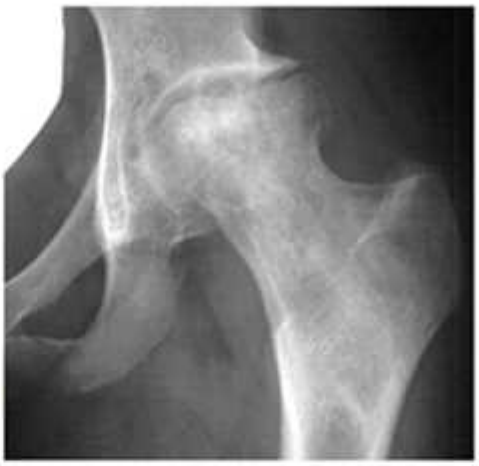
Associated with ***higher*** hemoglobin	Associated with ***lower*** hemoglobin
Painful episodes	Stroke
Acute chest syndrome	Priapism
Osteonecrosis	Leg Ulcers
Proliferative retinopathy	

Complications of Sickle Cell Disease



Sickle Cell – Avascular Necrosis





Sickle Cell – Dactylitis

Sickle Cell Anemia – Treatment

- Opiates and hydration for painful crises
- Pneumococcal vaccination
- Retinal surveillance
- Transfusion for serious manifestations (eg stroke); exchange transfusion
- Hydroxyurea
- Stem cell transplant

Treatment of Sickle cell anaemia

- Effective treatments are available to help relieve the symptoms and complications of sickle cell anemia, but in most cases there's no cure.

- The goal is to relieve the pain; prevent infections, eye damage, strokes and control complications if they occur.
- Pain medicine: acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and narcotics such as meperidine, morphine, oxycodone, and etc.
- Heating pads
- Hydroxyurea, Folic Acid
- Blood Transfusions

Prevention of Sickle cell anaemia

- Identify what can trigger the "Crisis" such as stress, avoid extremes of heat and cold weather, don't travel airplane that is not cabin pressurized
- Maintain healthy lifestyle habits
  - Eating healthy
  - Avoid dehydration
  - Exercise regularly
  - Get enough sleep and rest
  - Avoid alcohol and don't smoke
- Regular medical checkups and treatment are important

Summary

- Sickle-cell disease (SCD), or sickle-cell anaemia or drepanocytosis, is an autosomal co-dominant genetic blood disorder characterized by red blood cell that assume an abnormal, rigid, sickle shape.
- Pathogenesis: Basic molecular lesion, Mechanism of sickling, Reversible-irreversible sickling ,Factors determining rate of sickling
- Sickle cell trait is different from sickle cell anemia. People with sickle cell trait don't have the condition, but they have one of the genes that cause the condition

Thalassemia

- Thalassemia are a heterogenous group of genetic disorders of Hb synthesis characterized by a lack or decreased synthesis of globin chains

- Two major types of thalassemia:
  - Alpha (α) - Caused by defect in rate of synthesis of alpha chains.
  - Beta (β) - Caused by defect in rate of synthesis in beta chains.
- Alpha thalassemia usually caused by gene deletion; Beta thalassemia usually caused by mutation.
- Results in microcytic, hypochromic anemias of varying severity

BASICS - 3 Types of Hb

1. Hb A - 2α and 2β chains forming a tetramer

- 97% adult Hb
- Postnatal life Hb A replaces Hb F by 6 months

2. Fetal Hb – 2α and 2γ chains

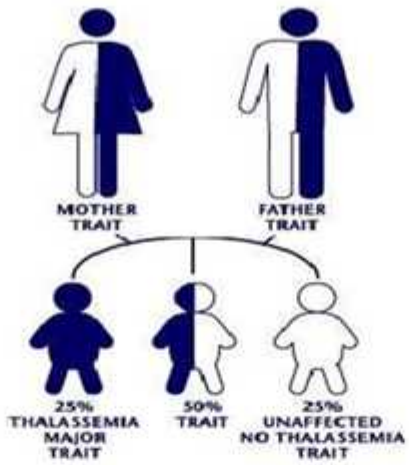
- 1% of adult Hb
- 70-90% at term. Falls to 25% by 1st month and progressively

3. Hb A2 – Consists of 2 α and 2 δ chains

- 1.5 – 3.0% of adult Hb

INHERITANCE

- Autosomal recessive
- Beta thal - point mutations on chromosome 11
- Alpha thal - gene deletions on chromosome 16



Classification of thalassemia

- If synthesis of α chain is suppressed – level of all 3 normal Hb A (2α ,2β),A2 (2α,2δ), F(2α ,2γ) reduced

– **alpha thalassemia**

- If β chain is suppressed- adult Hb is suppressed - **beta thalassemia**

α-thalassemia

Hb H (β_4)

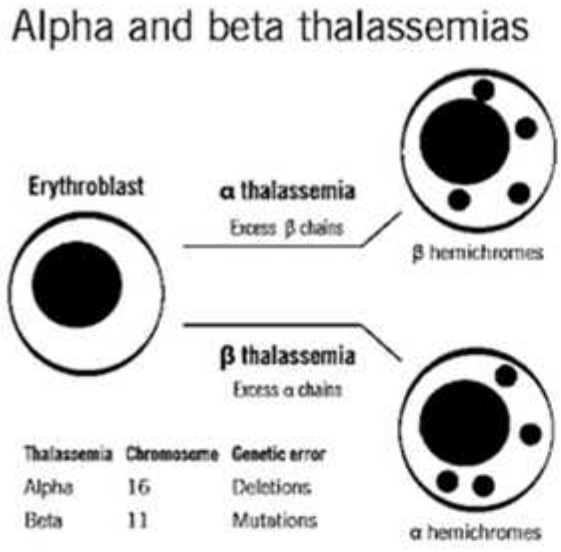
Hb-Bart's ($_4$)

β-thalassemia

- β^+ thal : reduced synthesis of β globin chain, heterozygous
- β^0 thal : absent synthesis of β globin chain, homozygous------ Hb A - absent

Hb F (α_{22})

Hb A_2 (α_2 δ_2)



Inclusion body
In HbH disease (a type of α thalassemia), excess β chains precipitate as hemoglobin H (β4) inclusion bodies in the cell. In β thalassemia major, excess α chains can also precipitate as inclusion bodies.

Heinz body
A type of inclusion body containing denatured hemoglobin. Classically associated with G6DP deficiency, these can be found in the thalassemias as well. Heinz bodies are typically larger than the inclusion bodies mentioned above. When a functional spleen is present, Heinz bodies lead to bite cells.

Howell-Jolly body
A type of inclusion body containing DNA. Like Heinz bodies, they are usually removed by splenic macrophages. Howell-Jolly bodies can be seen when red cells fail to fully mature or when a functional spleen is absent.

Because α chains dissociate into monomers more readily than β chains, the β chains form hemichromes at a faster rate; therefore making β thalassemia clinically more severe.

Classification of β Thalassemia

CLASSIFICATION	GENOTYPE	CLINICAL SEVERITY
β thal minor/trait	β/β+, β/β0	Silent
β thal intermedia	β+ /β+, β+/β0	Moderate
β thal major	β0/ β0	Severe

Classification OF α-Thalassemia

No. Of genes present	Genotype	Clinical classification
4 genes	αα/αα	Normal
3 genes	αα/- α	Silent carrier
2 genes	- α/- α or αα/- -	α thalassemia trait
1 gene	-α/- -	Hb H Ds
0 genes	- -/- -	Hb Barts / Hydrops fetalis

α-Thalassaemia Molecular Pathogenesis

- Defective synthesis of α-globin chains: HbA, HbA2 and HbF

1. Four α-gene deletion: Hb Bart's hydrops foetalis

2. Three α-gene deletion: HbH disease

3. Two α-gene deletion: α-thalassaemia trait

4. One α-gene deletion: α-thalassaemia trait (carrier)

β-Thalassaemia Molecular Pathogenesis

- β-thalassaemias are caused by decreased rate of β-chain synthesis resulting in reduced formation of HbA in the red cells.

i) *Transcription defect*

ii) *Translation defect*

iii) *mRNA splicing defect*

3 Types of β-Thalassaemia

1) Homozygous form

2) β-Thalassaemia intermedia

3) Heterozygous form

Pathophysiology

- Since ß chain synthesis reduced -
- 1. Gamma and delta δ_2 chain combines with normally produced α chains (Hb F (α_{22}) , Hb A_2 (α_2 δ_2) - Increased production of Hb F and Hb A_2
- 2. Relative excess of α chains → α tetramers forms aggregates →precipitate in red cells → inclusion bodies → premature destruction of maturing erythroblasts within the marrow (**Ineffective erythropoiesis**) or in the periphery (**Hemolysis**)→ destroyed in spleen

Anemia result from lack of adequate Hb A

→ tissue hypoxia→↑EPO production →

↑ erythropoiesis in the marrow and sometimes extramedullary → expansion of medullary cavity of various bones

Liver spleen enlarge → extramedullay

hematopoiesis

Clinical Features (Thal Major)

INFANTS:

- Age of presentation: 6-9 mo (Hb F replaced by Hb A)

- Progressive pallor and jaundice
- Cardiac failure
- Failure to thrive, gross motor delay
- Feeding problems
- Bouts of fever and diarrhea
- Hepatosplenomegaly

BY CHILDHOOD:

- Growth retardation
- Severe anemia-cardiac dilatation
- Transfusion dependant
- Icterus
- Changes in skeletal system

Clinical Features (Thal Intermedia)

- Moderate pallor, usually maintains Hb >6gm%
- Anemia worsens with pregnancy and infections (erythroid stress)
- Less transfusion dependant
- Skeletal changes present, progressive splenomegaly
- Growth retardation
- Longer survival than Thal major

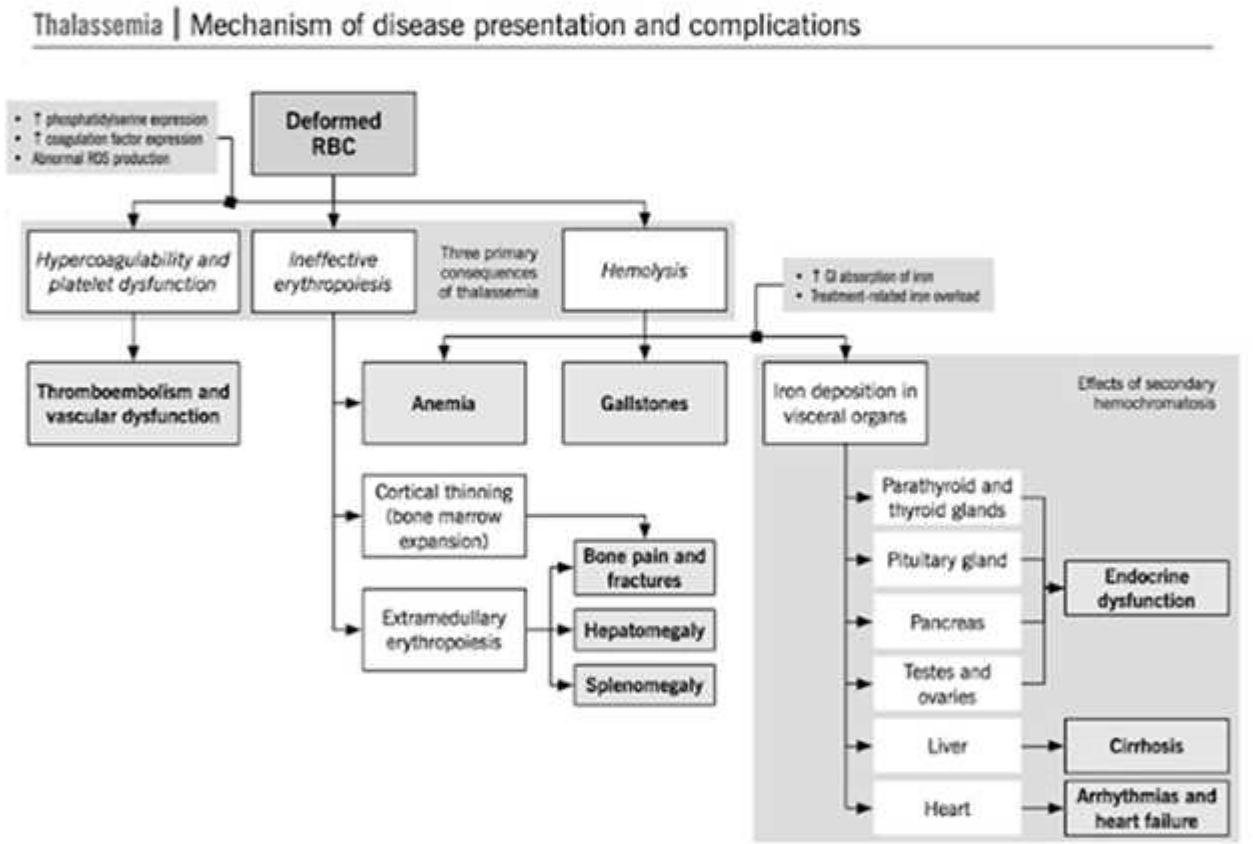
Clinical Features (Thal Minor)

- Usually **ASYMPTOMATIC**
- Mild pallor, no jaundice
- No growth retardation, no skeletal abnormalities, no splenomegaly
- **MAY PRESENT AS IRON DEFICIENCY ANEMIA** (Hypochromic microcytic anemia)

- Unresponsive/ refractory to Fe therapy
- Normal life expectancy

Prevention of Thalassaemia

- antenatal diagnosis
- amniocentesis and foetal DNA studied by PCR amplification technique for presence of genetic mutations of thalassaemias
- **Treatment-** blood transfusions (4-6 weekly), chelation therapy, folic acid supplement, Bone marrow transplantation



Summary

- Thalassemia are a heterogenous group of genetic disorders of Hb synthesis characterized by a lack or decreased synthesis of globin chains
  - Alpha (α) - Caused by defect in rate of synthesis of alpha chains.
  - Beta (β) - Caused by defect in rate of synthesis in beta chains.

Hereditary Acquired Anemia

- Hereditary haemolytic anaemias are usually the result of intracorpuscular defects.
- Classified into 2 groups:

1) Hereditary abnormalities of red cell membrane

2) Hereditary disorders of the interior of the red cells

A. Hereditary Abnormalities of Red Cell Membrane

3 important types of inherited red cell membrane defects:

1) Hereditary spherocytosis

2) Hereditary elliptocytosis (hereditary ovalocytosis)

3) Hereditary stomatocytosis.

Hereditary Spherocytosis
Pathogenesis

- The molecular abnormality in hereditary spherocytosis is a defect in proteins which anchor the lipid bilayer to the underlying cytoskeleton.

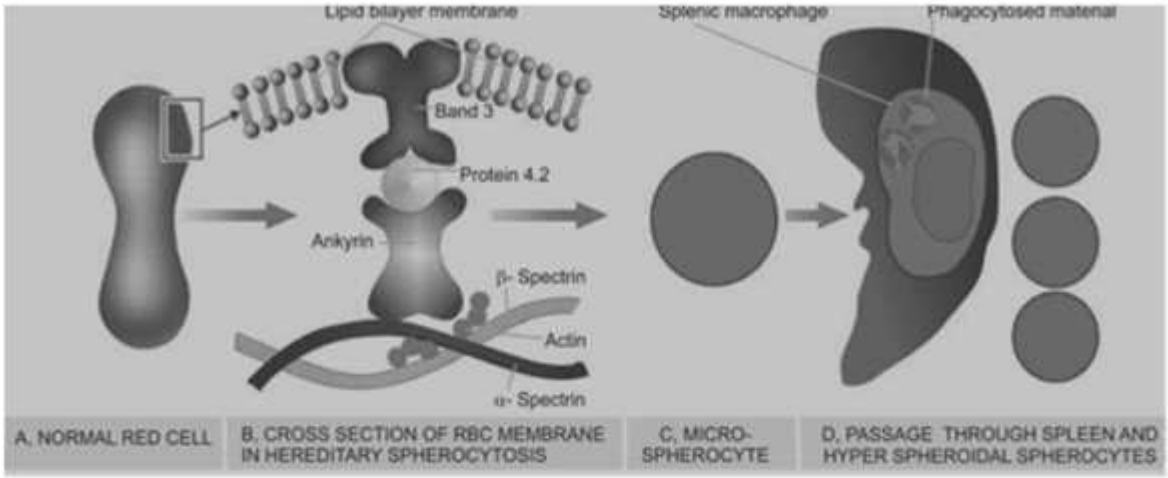
1) Spectrin deficiency: deficiency in the structural protein of the red cell membrane, spectrin

- Mutation in spectrin- α−*spectrin*- severe anaemia
- Mutation by β-*spectrin* results in mild Anaemia.

2) Ankyrin abnormality: defect in ankyrin, protein that binds protein 3 and spectrin

CLINICAL FEATURES

- *1. Anaemia* is usually mild to moderate.
- 2. *Splenomegaly* is a constant feature.
- 3. *Jaundice* occurs due to increased concentration of unconjugated (indirect) bilirubin in the plasma (also termed congenital haemolytic jaundice).
- 4. *Pigment gallstones* are



Hereditary Elliptocytosis (Hereditary Ovalocytosis)

- It is autosomal dominant disorder involving red cell membrane protein *spectrin.*

Hereditary Stomatocytosis

- Stomatocytes are cup-shaped RBCs having one surface concave and the other side as convex.
- This causes a central slit-like or mouth-like appearance of red cells.
- The underlying defect is in membrane protein *stomatin*

B. Hereditary Disorders of Red Cell Interior

- Inherited disorders involving the interior of the red blood cells are classified into 2 groups:

1. Red cell enzyme defects (Enzymopathies): These cause defective red cell metabolism involving 2 pathways

i) *Defects in the hexose monophosphate shunt*

ii) *Defects in the Embden-Meyerhof (glycolytic) pathway*

2. Disorders of haemoglobin (haemoglobinopathies):

These are divided into 2 subgroups:

i) *Structurally abnormal haemoglobin:* Examples are sickle syndromes and other haemoglobinopathies.

ii) *Reduced globin chain synthesis:* Common examples are various types of thalassaemias.

Red Cell Enzyme Defects (Enzymopathies) G6PD Deficiency

- Defects in hexose monophosphate shunt- G6PD deficiency

- G6PD gene is located on the X chromosome - affecting males

PATHOGENESIS

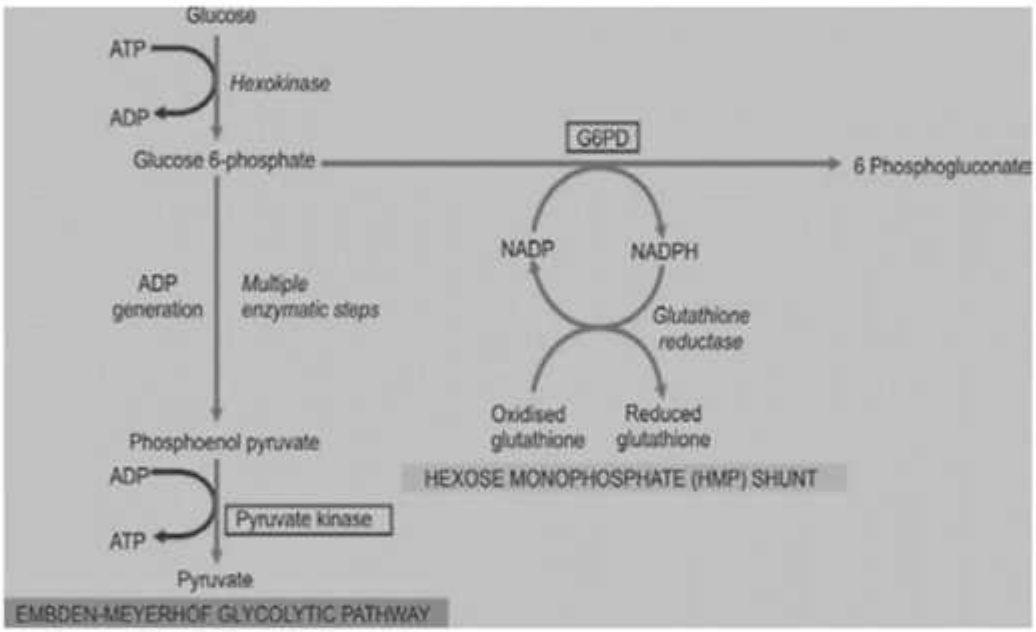
- Red blood cells are well protected against oxidant stress because of adequate generation of reduced glutathione via the hexose monophosphate shunt.
- Deficiency of G6PD

↓

- fail to develop adequate levels of reduced glutathione

↓

- Result in oxidation and precipitation of haemoglobin



PK Deficiency

- Pyruvate kinase (PK) deficiency is the only significant enzymopathy of the Embden-Meyerhof glycolytic pathway.
- The disorder is inherited as an autosomal recessive pattern. Heterozygote state – asymptomatic
- Homozygous individual presents during early childhood with anaemia, jaundice and splenomegaly.

Haemoglobinopathies

- Haemoglobin in RBCs may be abnormally synthesised due to inherited defects. These disorders may be of two types:

1) *Qualitative disorders* in which there is structural abnormality in synthesis of haemoglobin e.g. sickle cell syndrome, other haemoglobinopathies.

2) Quantitative disorders in which there quantitatively decreased globin chain synthesis of haemoglobin e.g. thalassaemias.

Summary

- Important types of inherited red cell membrane defects:

1) Hereditary spherocytosis

2) Hereditary elliptocytosis (hereditary ovalocytosis)

3) Hereditary stomatocytosis

- Hereditary spherocytosis is a common type of hereditary haemolytic anaemia- defect in proteins which anchor the lipid bilayer to the underlying cytoskeleton
- Hereditary elliptocytosis or hereditary ovalocytosis is another autosomal dominant disorder involving red cell membrane protein *spectrin*
- Hererditary stomatocytes are swollen red cells (overhydrated red cells) due to increased permeability to sodium and potassium. The affected patients have mild anaemia and splenomegaly.
- Inherited disorders involving the interior of the red blood cells are classified into 2 groups: **Red cell enzyme defects (Enzymopathies) and disorders of haemoglobin (haemoglobinopathies)**

Hemophilia

Normal Clotting

Response to vessle injury

1. Vasoconstriction to reduce blood flow

2. Platelet plug formation (von willebrand factor binds damaged vessle and platelets)

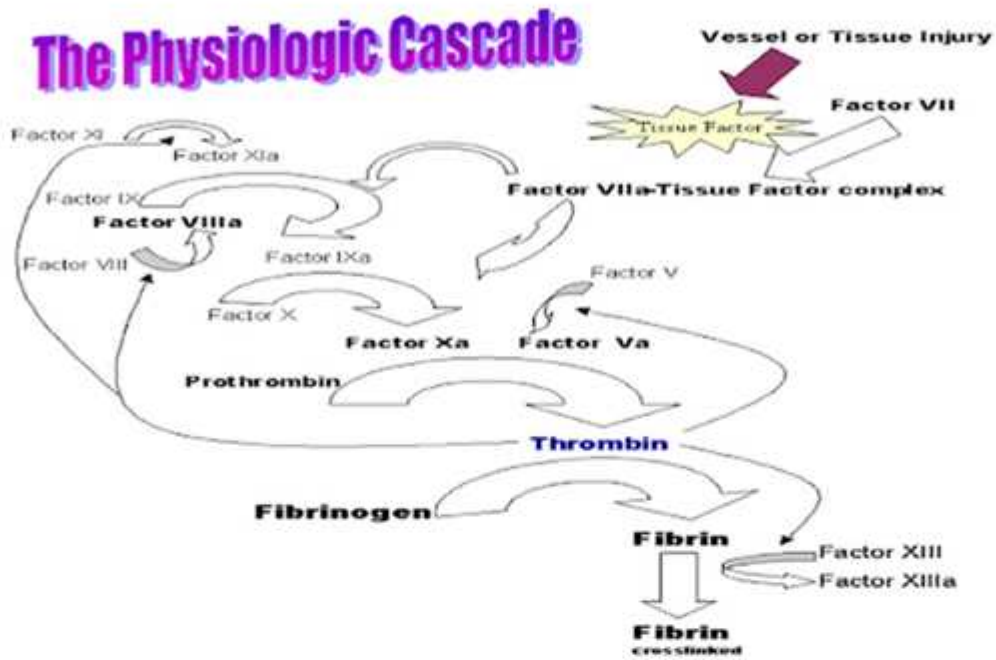
3. Activation of clotting cascade with generation of fibrin clot formation

4. Fibrinlysis (clot breakdown)

Clotting Cascade

Normally the ingredients, called factors, act like a row of dominoes toppling against each other to create a chain reaction.

If one of the factors is missing this chain reaction cannot proceed.



Hemophilia

Hemophilia is an inherited bleeding disorder in which there is a deficiency or lack of factor VIII (hemophilia A) or factor IX (hemophilia B)

COAGULATION DISORDERS: Disorders of plasma coagulation factors may have hereditary or acquired origin

HEREDITARY COAGULATION DISORDERS

1) Classic haemophilia or haemophilia A (due to inherited deficiency of factor VIII) sex-(X)- linked disorders

2) Christmas disease or haemophilia B (due to inherited deficiency of factor IX).

Types of Bleeding Disorders

- Hemophilia A (factor VIII deficiency)
- Hemophilia B (factor IX deficiency)
- von Willebrand Disease (vWD)
- Other

Inheritance of Hemophilia

- Hemophilia A and B are X-linked recessive disorders
- Hemophilia is typically expressed in males and carried by females
- Severity level is consistent between family members
- ~30 % of cases of hemophilia are new mutations

Haemophilia A

- It is the second most common hereditary coagulation disorder next to von Willebrand's disease occurring due to deficiency or reduced activity of factor VIII (anti-haemophilic factor).
- Inherited as a sex-(X-) linked recessive trait- manifest in males
- The frequency of haemophilia varies in different races, the highest incidence being in populations of Britain, Northern Europe and Australia.

Pathogenesis of Haemophilia A

- Haemophilia A is caused by quantitative reduction of factor VIII in 90% of cases, while 10% cases have normal or increased level of factor VIII with reduced activity
- Factor VIII synthesised hepatic parenchymal cells activate factor X (intrinsic coagulation pathway)
- Factor VIII-vWF complex
- 25% factor VIII level may develop bleeding, most symptomatic haemophilic patients have factor VIII levels below 5%.

Clinical Features of Haemophilia A

- Patients of haemophilia suffer from bleeding for hours or days after the injury.

TREATMENT

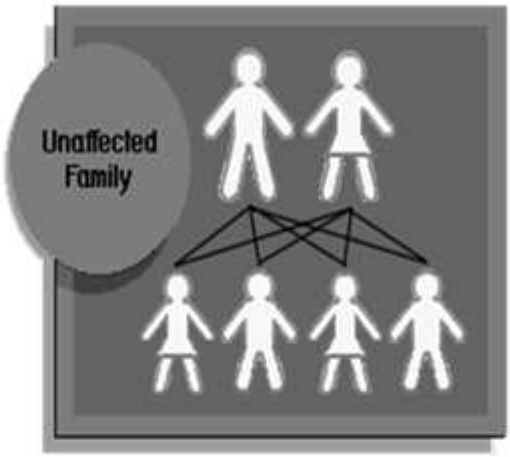
- Factor VIII replacement therapy,

Christmas Disease (Haemophilia B)

- Inherited deficiency of factor IX (Christmas factor or plasma thromboplastin component) produces Christmas disease or haemophilia B.
- **TREATMENT.** Therapy in symptomatic haemophilia B consists of infusion of either fresh frozen plasma or a plasma enriched with factor IX

Haemophilia Inheritance FVIII and FIX only

- Two chromosomes determine the sex of an individual, X and Y.
- Female XX
- Male XY



Father with Haemophilia

- Genetic defect causing haemophilia on that part of X chromosome not on Y chromosone
- Daughter of haemophiliac will inherit his X and be carrier.
- Sons of a haemophiliac will not be affected as they inherit fathers Y chromosome which does not carry FVIII or FIX gene.

Carrier Mother (one normal gene and one defective gene)

- Chances carrier mother passing defective gene to a child are 50:50.
- Each daughter has 50:50 chance being a carrier
- Each son has 50:50 chance of having haemophilia.

Spontaneous Mutation

In some 30% cases of haemophilia there is no known family history

Haemophilia is probably the result of spontaneous genetic mutation in these families.

Summary

HEREDITARY COAGULATION DISORDERS

- *Classic haemophilia or haemophilia A* (due to inherited deficiency of factor VIII) sex-(X)-linked disorders and *Christmas disease or haemophilia B* (due to inherited deficiency of factor IX
- Hemophilia A and B are X-linked recessive disorders
- Hemophilia is typically expressed in males and carried by females
- Haemophilia A is caused by quantitative reduction of factor VIII in 90% of cases, while 10% cases have normal or increased level of factor VIII with reduced activity
- Factor VIII replacement therapy

Diabetes Mellitus (DM)

- Chronic metabolic disorder
- Characterized by hyperglycemia due to deficiency of insulin or defective response of tissues to insulin

Classification of Diabetes Mellitus

Primary (idiopathic) DM

- Primary disorder by itself
- Type – I (Insulin dependent DM/ IDDM)
- Type – II (Non- Insulin dependent DM/NIDDM)

Secondary DM

- Due to identifiable cause – pancreatitis, endocrine disorder
- Gets corrected/ reversed when primary disorder is controlled

Etio-pathogenesis of Diabetes Mellitus

Normal Insulin Physiology

Regulated by 3 processes

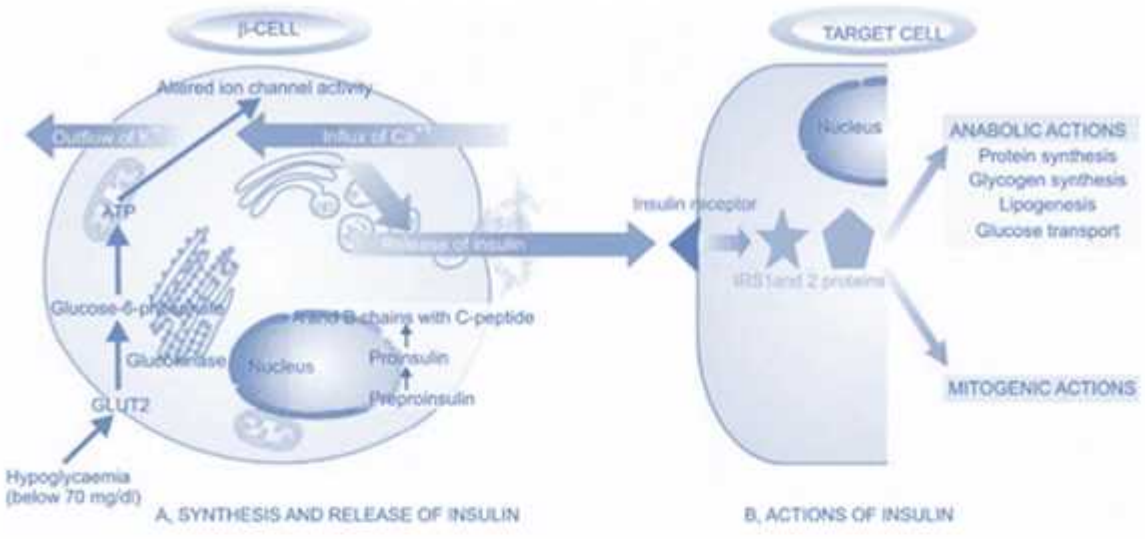
- Glucose production by liver
- Uptake and utilization of glucose by peripheral tissues

- Insulin secretion

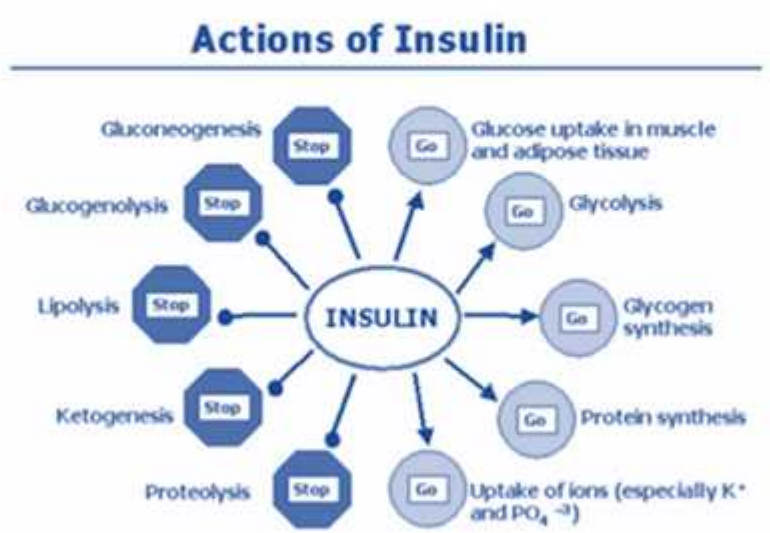
Normal Insulin Physiology

- Pre proinsulin – precursor for insulin
- Synthesized from insulin mRNA in rough ER of pancreatic β cells
- Delivered to golgi complex
- Series of proteolytic cleavage
- Pre proinsulin to pro insulin
- Finally to mature insulin + C- peptide
- Mature insulin + C- peptide – stored in equimolar concentration in secretory granules
- Glucose – important stimulus that triggers the syntheis & release of insulin
- Glucose taken up by pancreatic β cells through GLUT-2
- Immediate release of insulin
- Phase I of insulin secretion
- Released insulin is taken up by the insulin receptors present on the surface of tissues
- Series of intracellular reactions
- Activation of insulin dependent GLUT 4 transporter
- Uptake of glucose

Any defects in the above steps – Diabetes mellitus



Action of Insulin



Type I Diabetes Mellitus

- Insulin dependent DM
- Absolute lack of insulin
- Reduction in β cell mass
- Starts at childhood, becomes sever at puberty
- Dependent on daily injections of insulin

- Hence, insulin dependent DM

Involves 3 interconnected mechanism

- Genetic susceptibility
- Auto immunity
- Environmental factors

Genetic susceptibility

- Linked to race
- High among identical twins
- Susceptibility gene encodes class II antigen on MHC on chromosome 6p21 (HLA-D)
- Affects degree of immune response against pancreatic β cells

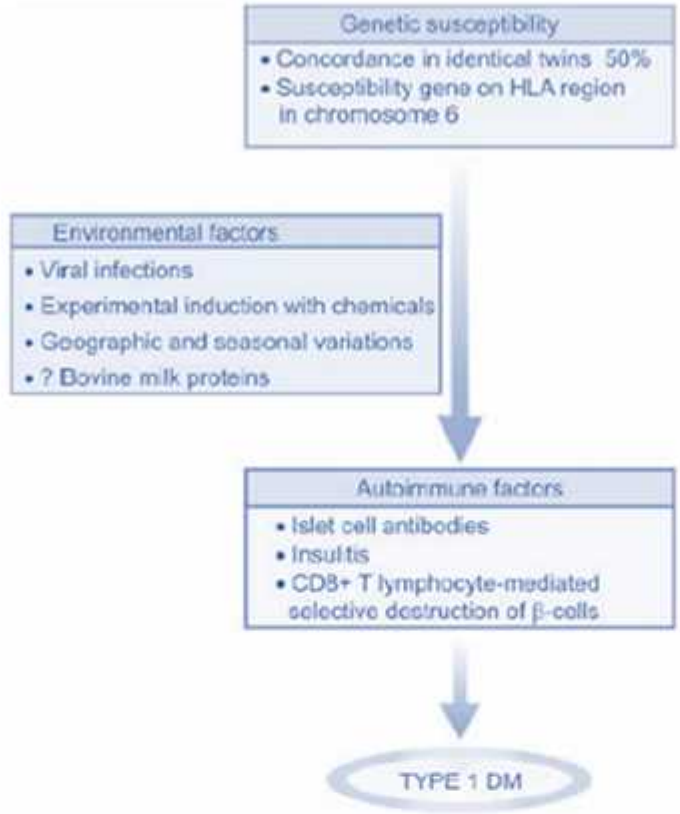
Auto immunity

- Onset of type I DM is abrupt
- Usually results from chronic auto immune attack of β cells
- Clinical manifestations occur after 90% of β cells mass has been destroyed by auto antibodies

Environmental factors

- Viral infections such as Measles, Mumps,
- Infection by COX sackie virus , Cytomegalo virus, Rubella virus
- Toxins – Pentamidine, Alloxan, Streptozotocin

Summary of pathogenesis of Type I DM



Type II DM

- Non insulin dependent DM
- Insulin therapy is not mandatory
- Disease is not linked to HLA gene
- Collection of multiple genetic defects
- Modified with environment factors

Pathogenesis of Type II DM

2 metabolic defects that characterize type II DM

- Derangement in β cell production of insulin
- Decreased response of peripheral tissues to insulin, rapid insulin resistance

Derangement in β cell production of insulin

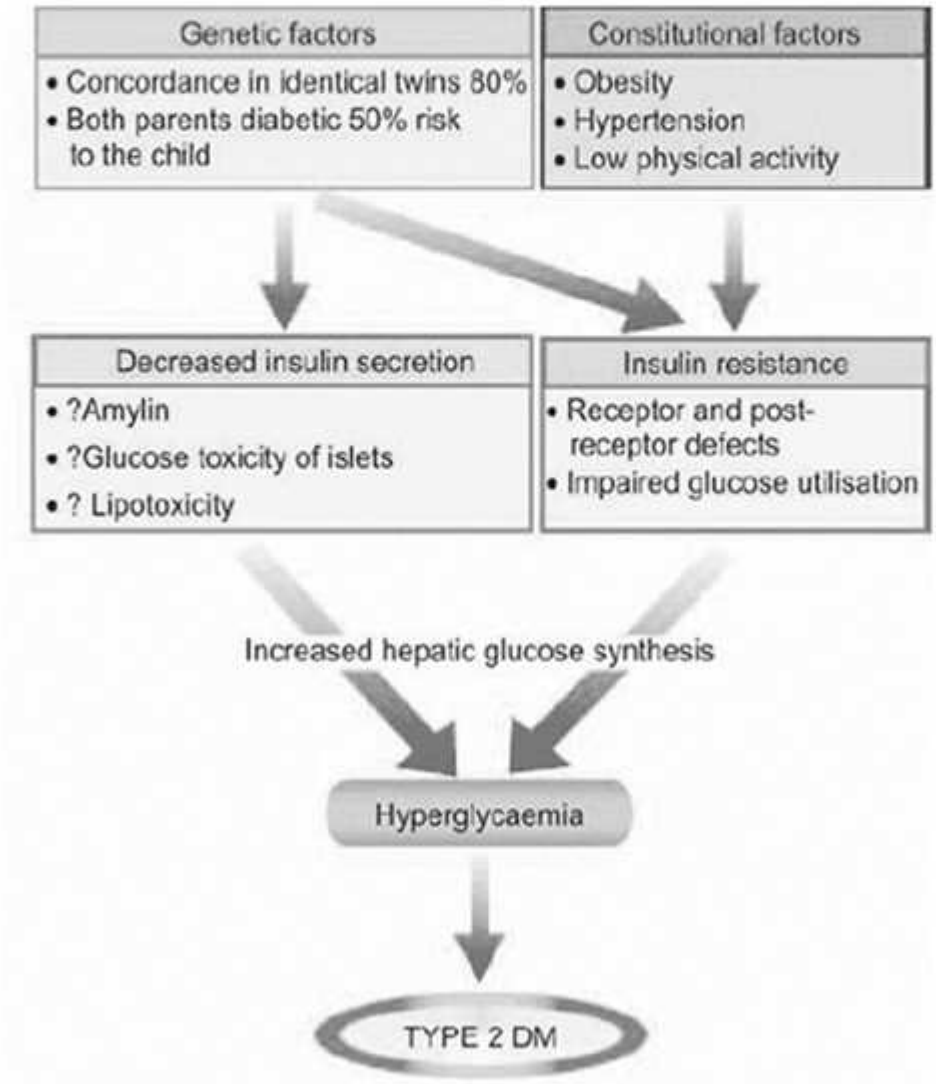
Decreased secretion of insulin from β cell Due to

- β cell damage on persistant stimulation
- Chronic hyperglycemia exhaust the ability of β cell to function

Decreased response of peripheral tissues to insulin, rapid insulin resistance

- Reduced responsiveness of peripheral tissues
- Leads to complications
- Insulin resistance due to reduction in no. of receptors
- Sensitivity of insulin receptor decreases in obesity & pregnancy

Summary of pathogenesis of type II DM



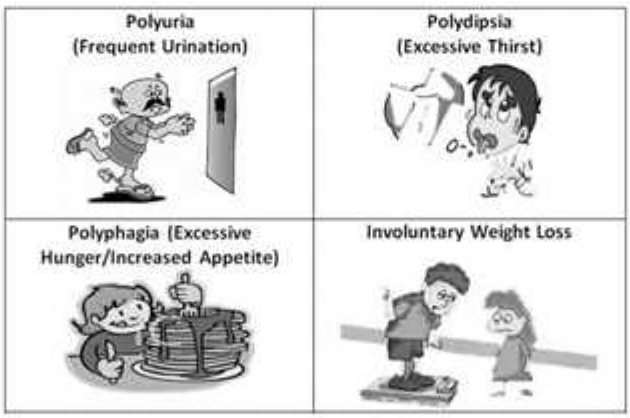
Summary

- Diabetes is a chronic metabolic disorder characterized by hyperglycemia due to deficiency of insulin or defective response of tissues to insulin
- DM is categorized as Type I and Type II
- Type I DM is dependent on insulin and occurs mainly due to the destruction of beta cells of pancreas
- Type II DM is independent of insulin and occurs either due to decreased insulin secretion or due to decreased sensitivity of insulin receptors

Clinical features of DM

Type I DM

- Low plasma insulin levels
- Poly uria
- Polyphagia
- Polydipsia
- Ketoacidosis
- Hypoglycemic episodes

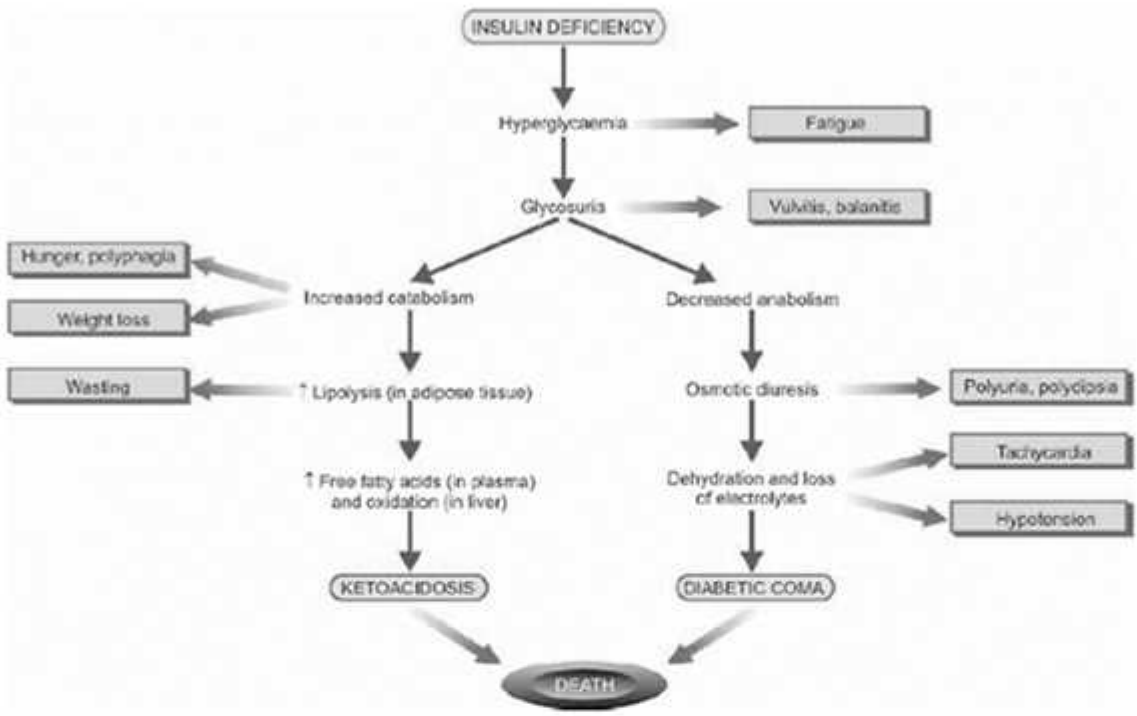


Type II DM

- Polyuria
- Polydipsia
- Unexplained weakness
- Plasma insulin normal to high

- Hyperosmolar non-ketotic coma

Pathophysiological basis of common signs and symptoms due to uncontrolled hyperglycaemia in diabetes mellitus



Complication of DM – Pathogenesis

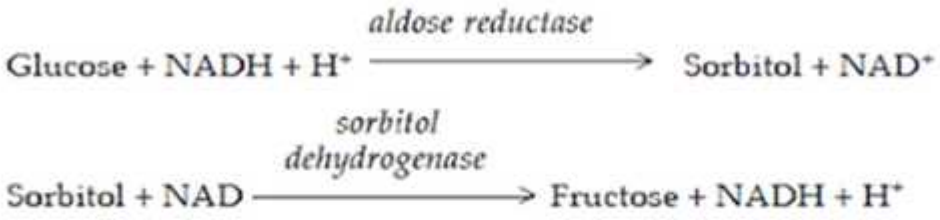
- Consequence of hyperglycemia
- Effects all most all the tissue
- Complications can either be acute or chronic
- 2 possible mechanism involved in development of complications
  - Non-enzymatic protein glycosylation
  - Polyol pathway mechanism

Non-enzymatic protein glycosylation

- Free amino group binds reversible to glucose
- Non enzymatic mechanism
- E.g. Hb with glucose (glycated Hb)
- Accumulates on collagen

- Irreversible advanced glycosylation end products (AGE)
- AGEs bind to receptors
- Biological & chemical changes

Polyol pathway mechanism



- Intracellular accumulation of sorbitol & fructose
- Entry of water inside cell
- Cellular swelling & damage
- Deficiency of myo inositol
- Harmful to retina

Acute metabolic complications

Diabetic ketoacidosis

- Complication of type I DM
- Due to shortage of insulin along with glucagon excess
- Failure to take insulin
- Lipolysis of adipose tissue
- Free fatty acids formed taken up by liver
- Converted ultimately to ketone bodies
- Excreted in urine

Hype osmolar non-ketotic coma

- Complication of Type II DM
- Due to sustained hyperglycemic diuresis

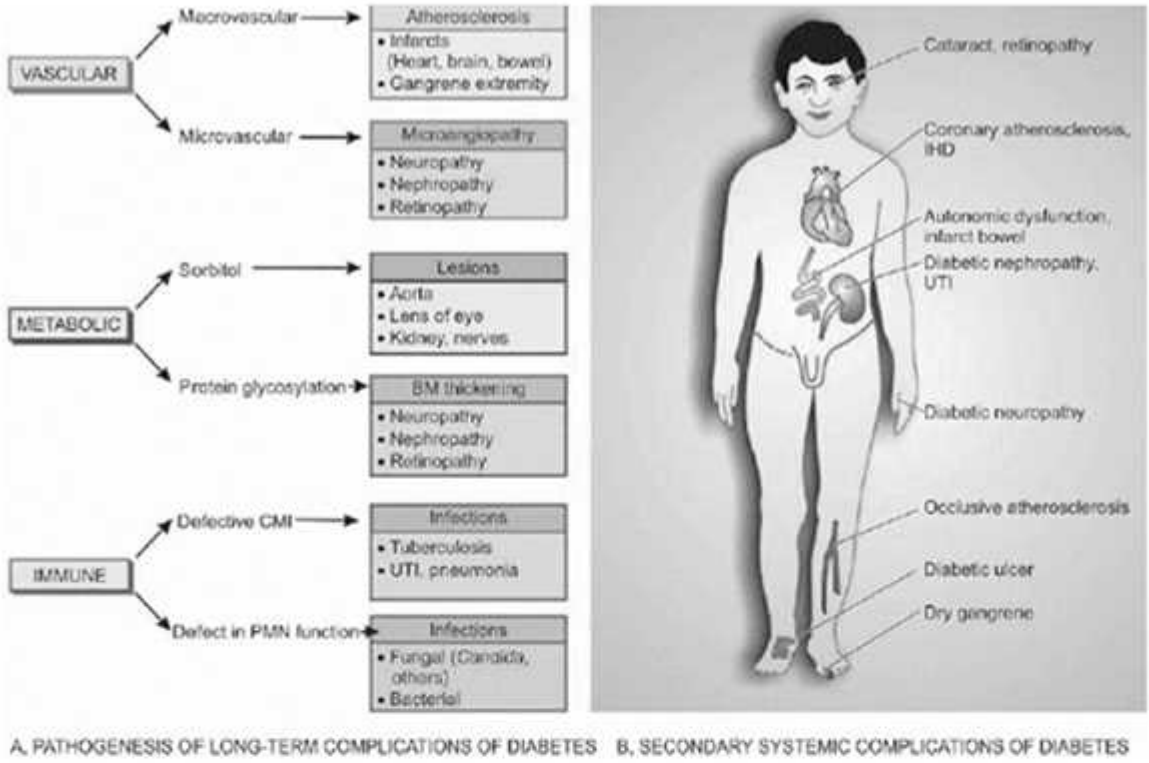
- Loss of glucose in urine
- Difficult to substitute the fluids lost of diuresis
- High viscosity of blood
- Bleeding complications
- Results in death

Hypoglycemic episodes

- Complication of type I & II DM
- Results from excess administration of insulin or oral hypoglycemic drugs
- May lead to permanent brain damage
- Worsening of diabetic control

Late systemic complications

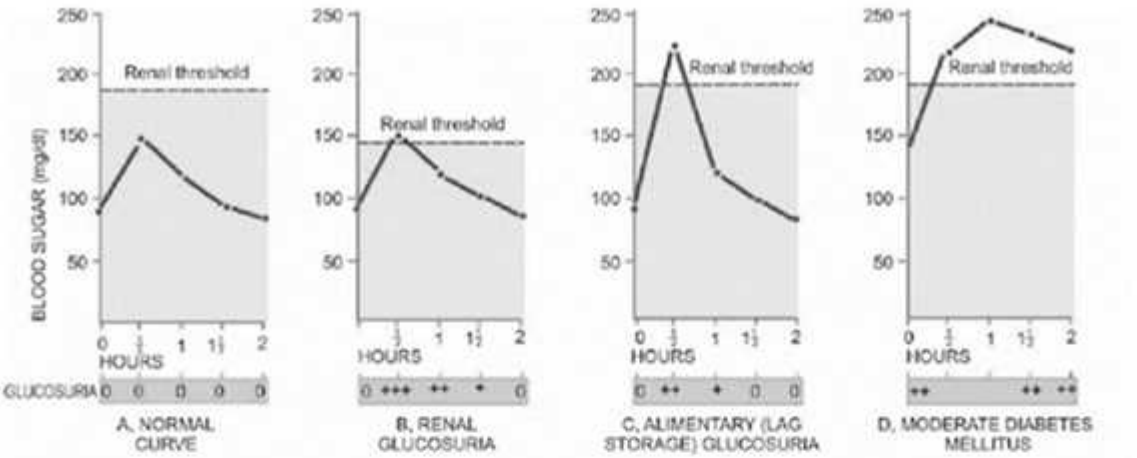
- Atherosclerosis
- Diabetic microangiopathy
- Diabetic nephropathy
- Diabetic neuropathy
- Diabetic retinopathy
- Infections



A. PATHOGENESIS OF LONG-TERM COMPLICATIONS OF DIABETES B. SECONDARY SYSTEMIC COMPLICATIONS OF DIABETES

Oral Glucose Tolerance Test (OGTT)

- Oral GTT is performed principally for patients with borderline fasting plasma glucose value (i.e. between 100-140 mg/dl)
- High carbohydrate diet for at least 3 days prior to the test
- overnight fast on the day of the test
- fasting blood sugar sample is first drawn
- 75 gm of glucose dissolved in 300 ml of water is given
- Blood and urine specimen are collected at half-hourly intervals for at least 2 hours
- Normal cut off value for fasting blood glucose level -100 mg/dl.
- Fasting blood glucose value in range of 100- 125 mg/dl - *impaired fasting glucose tolerance (IGT)*
- Fasting value of plasma glucose higher than 126 mg/dl
- 2-hour value after 75 gm oral glucose
- Higher than 200 mg/dl - *diabetics*



The glucose tolerance test, showing blood glucose curves (venous blood glucose) and glucosuria after 75 gm of oral glucose

Summary

- Persistent hyperglycemia is associated with diabetic complications
- Non-enzymatic glycation and polyol pathway mechanism are the two main mechanisms involved in the development of complications of DM

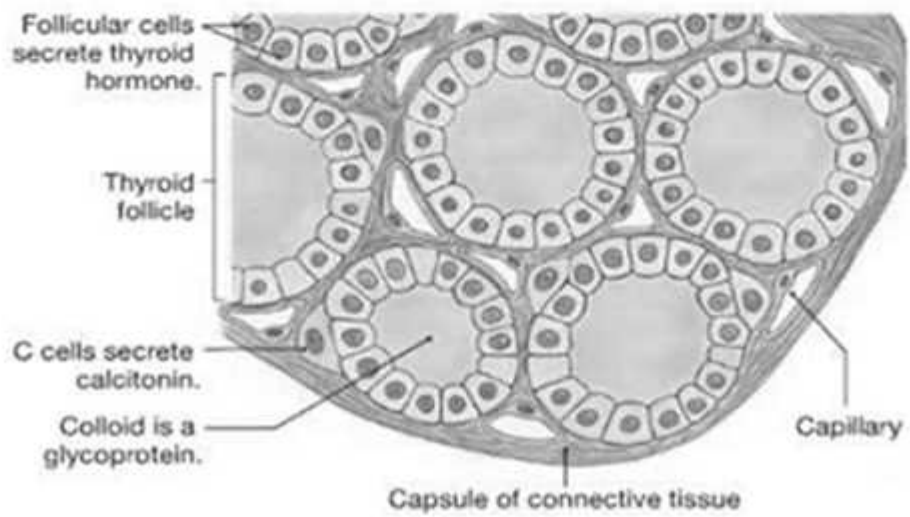
Acute metabolic complication and late systemic complication are major complications of DM

- Oral GTT is performed principally for patients with borderline fasting plasma glucose value (i.e. between 100-140 mg/dl)

Thyroid Disease

Thyroid Gland

- The thyroid gland in an adult weighs 15-40 gm and is composed of two lateral lobes connected in the midline by a broad isthmus which may have a pyramidal lobe extending upwards



HYPERTHYROIDISM (THYROTOXICOSIS)

- Hyperthyroidism, also called thyrotoxicosis, is a hypermetabolic clinical and biochemical state caused by excess production of thyroid hormones

ETIOPATHOGENESIS

- 3 most common causes are:

1) Graves' disease (diffuse toxic goitre),
2) toxic multinodular goitre
3) toxic adenoma

Other causes

- hypersecretion of pituitary TSH by a pituitary tumour
- hypersecretion of TRH
- Thyroiditis
- metastatic tumours of the thyroid
- struma ovarii
- congenital hyperthyroidism in the newborn of mother with Graves' disease
- hCG-secreting tumours due to mild thyrotropic effects of hCG (e.g. hydatidiform mole, choriocarcinoma and testicular tumours),
- Excessive doses of thyroid hormones or iodine called *jodbasedow disease*

CLINICAL FEATURES

- Fatigue
- heat intolerance
- sweating
- weight loss despite good appetite
- shakiness
- inappropriate anxiety

- palpitations of the heart
- shortness of breath,
- tetchiness and agitation,
- poor sleep
- thirst
- nausea
- increased frequency of defecation

Hypothyroidism

- It is a hypometabolic clinical state resulting from inadequate production of thyroid hormones for prolonged periods, or rarely, from resistance of the peripheral tissues to the effects of thyroid hormones

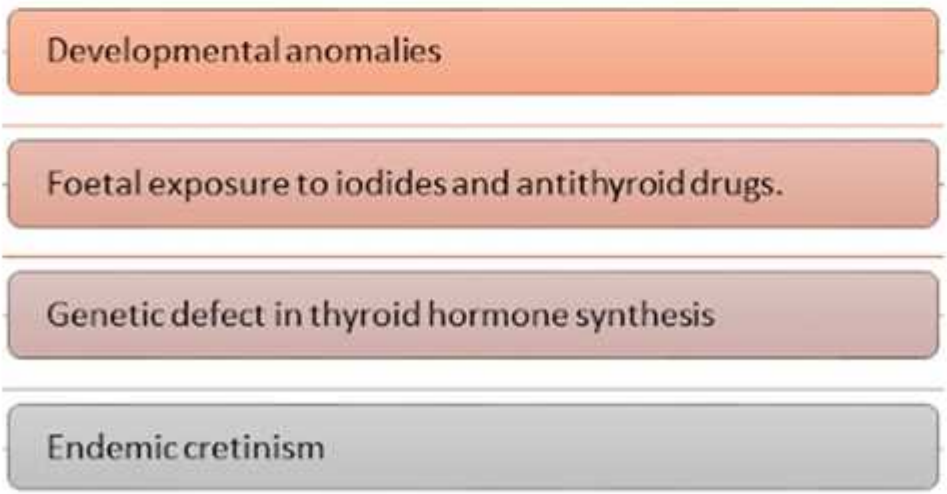
1. Cretinism or *congenital hypothyroidism* -infancy and childhood.

2. *Myxoedema* - adulthood

Cretinism

- Hypothyroidism present at birth or developing within first two years of postnatal life.

ETIOPATHOGENESIS. The causes of congenital hypothyroidism are as follows:



CLINICAL FEATURES (c'd)

- Dry, pale & mottled skin
- Low hair line & dry, scanty hair
- Hypothermia & peripheral cyanosis
- Hypercarotenemia
- Growth failure
- Retarded bone age
- Stumpy fingers & broad hands

Myxoedema

- The adult-onset severe hypothyroidism causes myxoedema

ETIOPATHOGENESIS

1. Ablation of the thyroid by surgery or radiation.

2. Autoimmune (lymphocytic) thyroiditis (termed primary idiopathic myxoedema).

3. Endemic or sporadic goitre.

4. Hypothalamic-pituitary lesions.

5. Thyroid cancer.

6. Prolonged administration of anti-thyroid drugs.

7. Mild developmental anomalies and dyshormonogenesis

CLINICAL FEATURES

- cold intolerance
- mental and physical lethargy
- constipation
- slowing of speech and intellectual function
- puffiness of face
- loss of hair and altered texture of the skin

THYROIDITIS

- Inflammation of the thyroid- Due to non-infectious causes

Classification of Thyroiditis

I. Acute thyroiditis:

1. Bacterial infection e.g. *Staphylococcus*, *Streptococcus*.

2. Fungal infection e.g. *Aspergillus*, *Histoplasma*, *Pneumocystis*.

3. Radiation injury

II. Subacute thyroiditis:

1. Subacute granulomatous thyroiditis (de Quervain's thyroiditis, giant cell thyroiditis, viral thyroiditis)

2. Subacute lymphocytic (postpartum, silent) thyroiditis

3. Tuberculous thyroiditis

III. Chronic thyroiditis:

1. Autoimmune thyroiditis (Hashimoto's thyroiditis or chronic lymphocytic thyroiditis)

2. Riedel's thyroiditis (or invasive fibrous thyroiditis)

HASHIMOTO'S (AUTOIMMUNE, CHRONIC LYMPHOCYTIC) THYROIDITIS

- Hashimoto's thyroiditis, also called diffuse lymphocytic thyroiditis, struma lymphomatosa or goitrous autoimmune thyroiditis

ETIOPATHOGENESIS

1. autoimmune disease association
2. Immune destruction of thyroid cells
3. Detection of autoantibodies
4. Inhibitory TSH-receptor antibodies
5. Genetic basis

GRAVES' DISEASE (DIFFUSE TOXIC GOITRE)

- Graves' disease, also known as Basedow's disease, primary hyperplasia, exophthalmic goitre, and diffuse toxic goitre

- Characterised by a triad of features:

1. Hyperthyroidism (thyrotoxicosis)

2. Diffuse thyroid enlargement

3. Ophthalmopathy

ETIOPATHOGENESIS OF GRAVES' DISEASE

- **1. Genetic factor association:** HLA-DR3 (Hashimoto's thyroiditis has both HLA-DR3 and HLA-DR5 association) *CTLA-4* and *PTPN22* (a T-cell regulatory gene).

- **2. Autoimmune disease association: Other factors.** Besides these two factors, Graves' disease has higher prevalence in women (7 to 10 times), and association with emotional stress and smoking

- **3. Other factors**

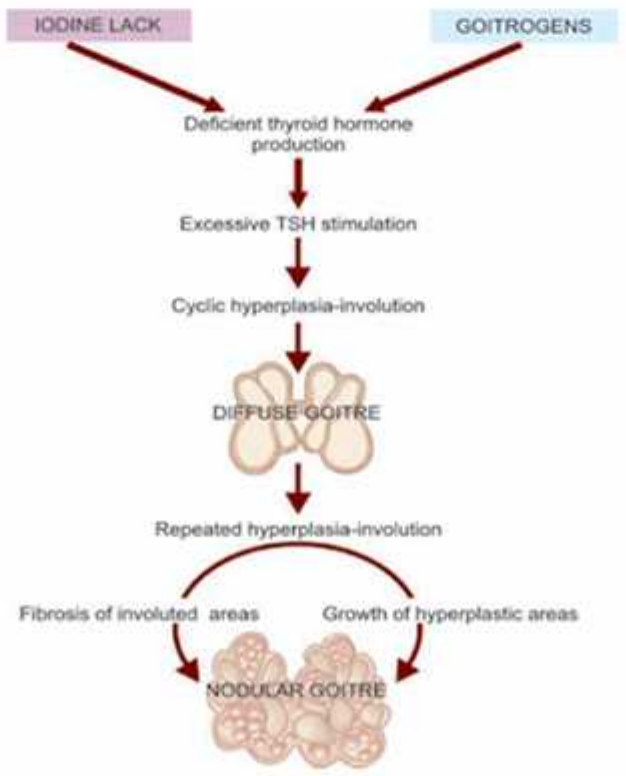
- **4. Autoantibodies: TSI, TGI, TBII**

GOITRE

- Thyroid enlargement caused by compensatory hyperplasia and hypertrophy of the follicular epithelium -thyroid hormone deficiency

Pathogenesis of Goitre

- Nodular goitre is generally regarded as the end-stage of long-standing simple goitre



ETIOLOGY OF GOITRE

- Goitre occurs in 2 forms: endemic, and non-endemic or sporadic

Endemic goitre:

Mountainous regions-iodine content of drinking water and food

_ Genetic factors, *Goitrogens*

Sporadic (non-endemic) goitre:

_ Suboptimal iodine intake in conditions of increased demand as in puberty and pregnancy.

_ Genetic factors.

_ Dietary goitrogenes.

_ Hereditary defect in thyroid hormone synthesis and transport

_ Inborn errors of iodine metabolism

Nodular Goitre (Multinodular Goitre, Adenomatous Goitre)

- It is the end-stage of long-standing simple goitre. It is characterised by most extreme degree of tumour-like enlargement of the thyroid gland and characteristic nodularity

TABLE 27.2: Contrasting Features of Simple and Nodular Goitre.

Feature	Diffuse Goitre	Nodular Goitre
1. *Nomenclature*	Simple goitre, hyperplastic goitre, nontoxic goitre	Multinodular, adenomatous goitre
2. *Etiology*	Graves' disease, thyroiditis, puberty	Endemic thyroiditis, cancer
3. *Pathogenesis*	Hyperplasia-involution	Repeated cycles of hyperplasia with growth and involution with fibrosis
4. *Composition*	Cellular-rich	Colloid-rich
5. *Gross*	Moderate, symmetric, diffuse enlargement, colloid-filled follicles, gelatinous	Nodular asymmetric, haemorrhages, scarring, cystic change, calcification
6. *Microscopy*	Hyperplastic phase: papillary infoldings, Involution stage: large colloid filled follicles with flat epithelium	Incomplete encapsulation, nodularity, variable-sized follicles, fibrous scarring, haemorrhages, calcification, cyst formation
7. *Functional status*	Hyperthyroidism, euthyroid	Hypothyroidism, euthyroid

THYROID TUMOURS

- Tumours of the thyroid are of follicular epithelial origin; a few arise from parafollicular C-cells
- thyroid carcinoma is the most common type

FOLLICULAR ADENOMA

- In adult women

- an adenoma is small (up to 3 cm in diameter) and spherical.

THYROID CANCER

	Feature	Papillary Carcinoma	Follicular Carcinoma	Medullary Carcinoma	Anaplastic Carcinoma
1.	*Frequency*	75-80%	10-20%	5%	5%
2.	*Age*	All ages	Middle to old age	Middle to old age; familial too	Old age
3.	*Female/male ratio*	3:1	2.5:1	1:1	1.5:1
4.	*Relation to radiation*	Maximum	Present	None	Present
5.	*Genetic alterations*	*RET* gene over-expression, *NTRK* gene rearrangement	*RAS* mutation, *PAX-PPAR γ1* fusion	*RET* point mutation	*p53* loss, β-catenin mutation
6.	*Cell of origin*	Follicular	Follicular	Parafollicular	Follicular
7.	*Gross*	Small, multifocal	Moderate size, nodular	Moderate size	Invasive growth
8.	*Pathognomonic microscopy*	Nuclear features, papillary pattern	Vascular and capsular invasion	Solid nests, amyloid stroma	Undifferentiated, spindle-shaped, giant cells
9.	*Regional metastases*	Common	Rare	Common	Common
10.	*Distant metastases*	Rare	Common	Rare	Common
11.	*10-year survival*	80-95%	50-70%	60-70%	5-10% (median survival about 2 months)

Summary

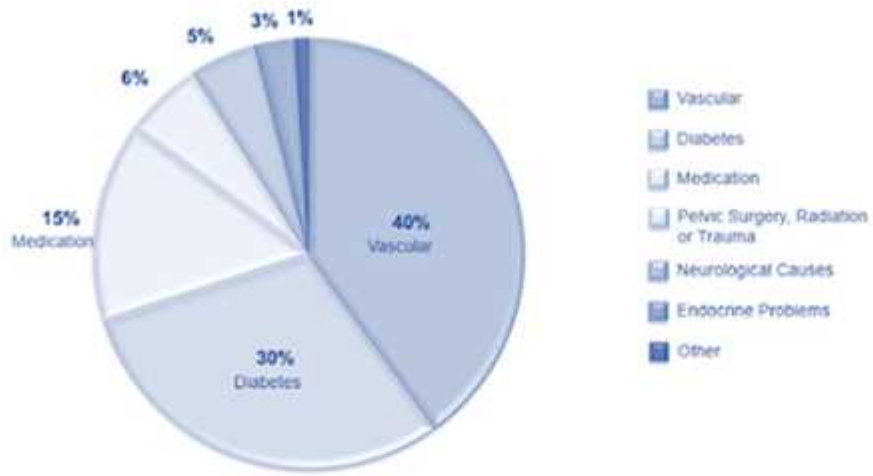
- Hyperthyroidism, also called thyrotoxicosis, is a hypermetabolic clinical and biochemical state caused by excess production of thyroid hormones
- Hypothyroidism is a hypometabolic clinical state resulting from inadequate production of thyroid hormones for prolonged period
- Thyroiditis -Inflammation of the thyroid- Due to non-infectious causes
- Goitre-Thyroid enlargement caused by compensatory hyperplasia and hypertrophy of the follicular epithelium -thyroid hormone deficiency
- Tumours of the thyroid are of follicular epithelial origin; a few arise from parafollicular C-cells

Erectile Dysfunction (ED)

Erectile dysfunction is defined as “the failure to achieve a penile erection to allow for satisfactory sexual intercourse”

Patients may refer to it as impotence

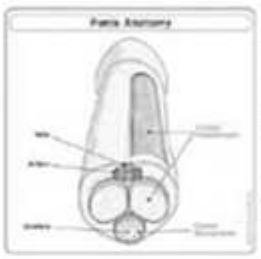
Main Causes of Erectile dysfunction



Etiology of Erectile dysfunction

- **Psychogenic**
- **Vasculogenic : -** Cardiovascular disease - Hypertension - Diabetes mellitus - Major surgery or radiotherapy (pelvis or etroperitoneum).
- **Neurogenic Central causes** - Multiple sclerosis - Parkinson's disease - Tumors - Stroke - Spinal cord disorders(disc disease) Peripheral causes - Diabetes mellitus - Alcoholism - Polyneuropathy - Surgery (pelvis or retroperitoneum).
- **Anatomical / structural** - Peyronie's disease - Penile fracture - Congenital curvature of the penis
- **Hormonal - Hypogonadism** - Hyperprolactinemia - Hyper-and hypothyroidism - Cushing's disease.
- **Drug-induced** - Antihypertensives (beta-blocker,thiazide and clonidine .less with ACE inhibitors) - Antidepressants (tricyclic antidepressants and MAO inihibitor) - Antipsychotics - Antiandrogens - Antihistamines - Recreational drugs (Heroin and cocaine)

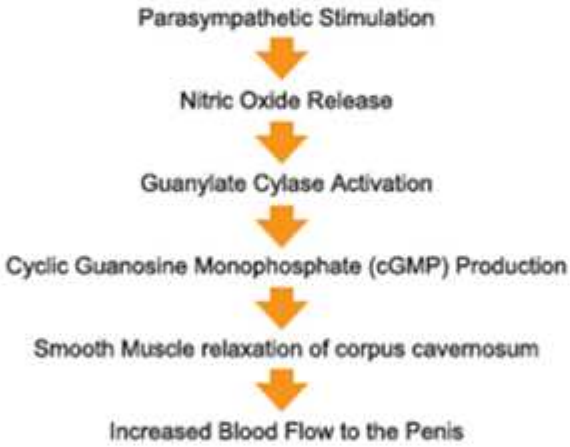
How Dose Erection Normally Happen?



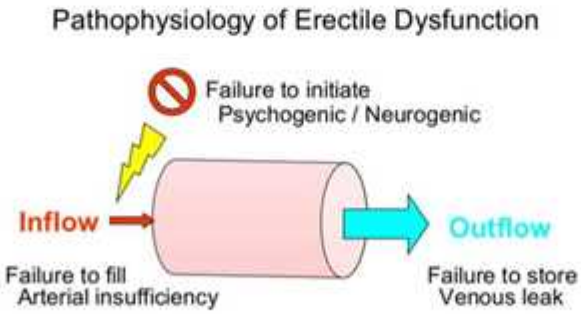
The brain starts the changes that will produce an erection

- As a result of psychological or physical stimulation, the brain sends messages through the nervous system to the penis.
- These messages relax the smooth muscles in the blood vessel walls of the corpus cavernosum, causing them to open wider.
- When this happens, more blood flows through the vessels, filling the corpus cavernosum.
- At the same time, the veins that carry blood away from the penis shut down, causing an increase in blood pressure in the penis.
- The blood that is trapped within the corpus cavernosum causes the penis to become hard and erect.

Process of Erection



Pathophysiology of Erectile Dysfunction



- Any single abnormality or combination of abnormalities of the four systems necessary for a normal penile erection
- Vascular, neurologic, or hormonal etiologies of erectile dysfunction are collectively referred to as *organic erectile dysfunction*

- Patients who do not respond to psychogenic stimuli have *psychogenic erectile dysfunction*
- Diseases that compromise vascular flow to the corpora cavernosum (e.g., peripheral vascular disease, arteriosclerosis, and essential hypertension) increases incidence of ED
- Diseases that impair nerve conduction to the brain (e.g., spinal cord injury or stroke) or conditions that impair peripheral nerve conduction to the penile vasculature
- Diseases associated with hypogonadism, primary or secondary, result in subphysiologic levels of testosterone, which cause diminished sexual drive (decreased libido) and secondary erectile dysfunction
- Vasoconstrictor effect of cigarette smoking may compromise blood flow to the corpora and decrease cavernosal filling
- Excessive ethanol intake may lead to androgen deficiency, peripheral neuropathy

Clinical Presentation of Erectile Dysfunction

CLINICAL PRESENTATION: ERECTILE DYSFUNCTION

General

- ☐ Men are affected emotionally in many different ways
- ☐ Depression
- ☐ Performance anxiety
- ☐ Marital difficulties and avoidance of sexual intimacy (patients are often brought to a physician by their partners)
- ☐ Nonadherence to medications patient believes are causing erectile dysfunction

Symptoms

- ☐ Impotence or inability to have sexual intercourse

Summary

- Erectile dysfunction is defined as "the failure to achieve a penile erection to allow for satisfactory sexual intercourse"
- It can occur due to various causes like psychogenic, vasculogenic and neurogenic
- Failure to initiate psychogenic or neurogenic impulse or failure to increase arterial blood pressure may result in ED
- ED may ultimately lead to impotence

Infertility

- The inability to conceive following unprotected sexual intercourse
  - 1 year (age < 35) or 6 months (age >35)
  - Affects 15% of reproductive couples
    - 6.1 million couples
  - Men and women equally affected
- Reproductive age for women
  - Generally 15-44 years of age
  - Fertility is approximately halved between 37th and 45th year due to alterations in ovulation
  - 20% of women have their first child after age 30
  - 1/3 of couples over 35 have fertility problems
    - Ovulation decreases
    - Health of the egg declines

Primary infertility

- a couple that has never conceived

Secondary infertility

- infertility that occurs after previous pregnancy regardless of outcome

Requirements for Conception

- Production of healthy egg and sperm
- Unblocked tubes that allow sperm to reach the egg
- The sperms ability to penetrate and fertilize the egg
- Implantation of the embryo into the uterus
- Finally a healthy pregnancy

Causes for infertility

- **Male**
  - ETOH
  - Drugs
  - Tobacco
  - Health problems
  - Radiation/Chemotherapy
  - Age
  - Enviromental factors
    - Pesticides
    - Lead
- **Female**
  - Age
  - Stress
  - Poor diet
  - Athletic training
  - Over/underweight
  - Tobacco
  - ETOH
  - STD's
  - Health problems

Causes of Infertility

- Anovulation (10-20%)
- Anatomic defects of the female genital tract (30%)

- Abnormal spermatogenesis (40%)
- Unexplained (10%-20%)

Evaluation of the Infertile couple

- History and Physical exam
- Semen analysis
- Thyroid and prolactin evaluation
- Determination of ovulation
  - Basal body temperature record
  - Serum progesterone
  - Ovarian reserve testing
- Hysterosalpingogram

Abnormalities of Spermatogenesis

Male Factor

- 40% of the cause for infertility
- Sperm is constantly produced by the germinal epithelium of the testicle
  - Sperm generation time 73 days
  - Sperm production is thermoregulated
    - 1° F less than body temperature
- Both men and women can produce anti-sperm antibodies which interfere with the penetration of the cervical mucus

Semen Analysis (SA)

- Obtained by masturbation
- Provides immediate information
  - Quantity
  - Quality

- Density of the sperm

- Abstain from coitus 2 to 3 days
- Collect all the ejaculate
- Analyze within 1 hour
- A normal semen analysis excludes male factor 90% of the time

Normal Values for SA

Volume - 2.0 ml or more

Sperm Concentration - 20 million/ml or more

Motility - 50% forward progression

25% rapid progression

Viscosity - Liquification in 30-60 min

Morphology - 30% or more normal forms

pH - 7.2-7.8

WBC - Fewer than 1 million/ml

Causes for male infertility

- 42% varicocele
  - repair if there is a low count or decreased motility
- 22% idiopathic
- 14% obstruction
- 20% other (genetic abnormalities)

Abnormal Semen Analysis

- Azospermia
  - Klinefelter's (1 in 500)
  - Hypogonadotropic-hypogonadism

- Ductal obstruction (absence of the Vas deferens)

- Oligospermia
  - Anatomic defects
  - Endocrinopathies
  - Genetic factors
  - Exogenous (e.g. heat)

- Abnormal volume
  - Retrograde ejaculation
  - Infection
  - Ejaculatory failure

Evaluation of Ovulation

Menstruation

- Ovulation occurs 13-14 times per year
- Menstrual cycles on average are Q 28 days with ovulation around day 14
- Luteal phase
  - dominated by the secretion of progesterone
  - released by the corpus luteum
- Progesterone causes
  - Thickening of the endocervical mucus
  - Increases the basal body temperature (0.6° F)
- Involution of the corpus luteum causes a fall in progesterone and the onset of menses

Ovulation

- A history of regular menstruation suggests regular ovulation
- The majority of ovulatory women experience
  - fullness of the breasts

- decreased vaginal secretions
- abdominal bloating
- mild peripheral edema
- slight weight gain
- depression

- Absence of PMS symptoms may suggest anovulation

Anovulation

Symptoms

- Irregular menstrual cycles
- Amenorrhea
- Hirsuitism
- Acne
- Galactorrhea
- Increased vaginal secretions

Evaluation*

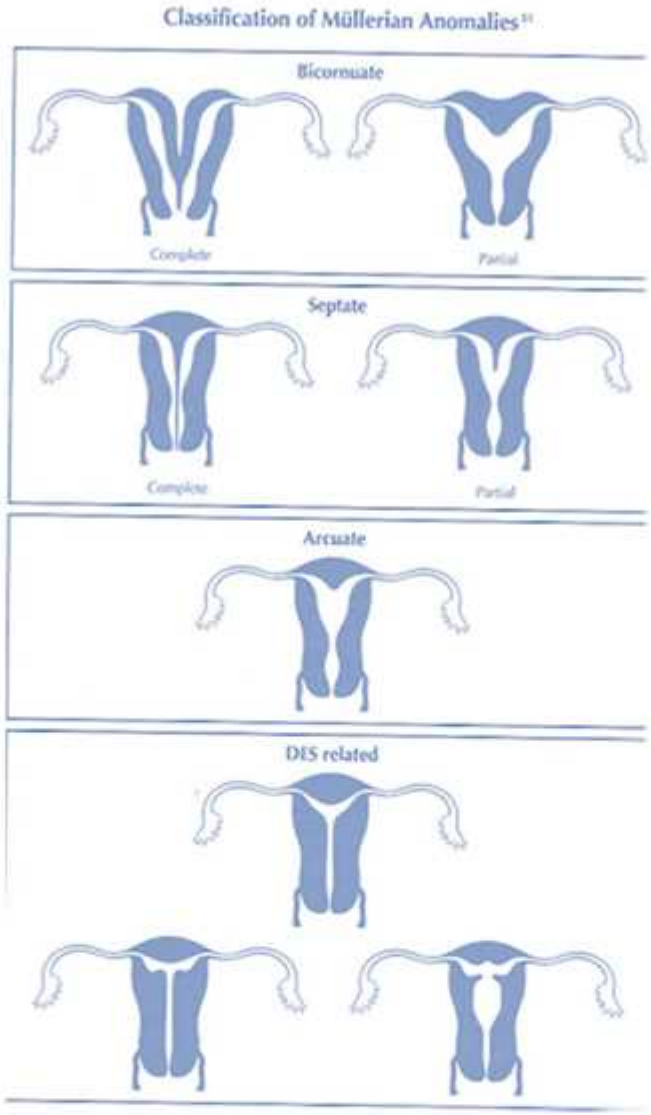
- Follicle stimulating hormone
- Lutenizing hormone
- Thyroid stimulating hormone
- Prolactin
- Androstenedione
- Total testosterone
- DHEAS

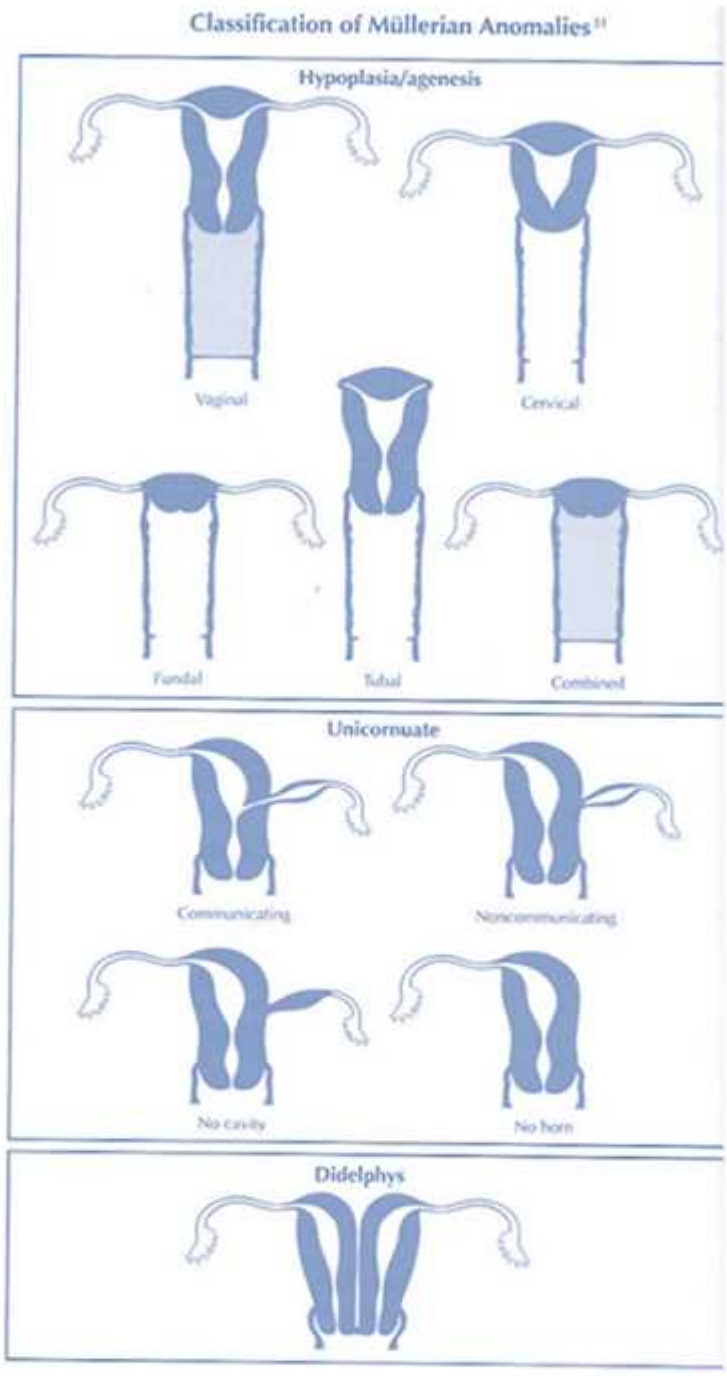
*Order the appropriate tests based on the clinical indications

Anatomic Disorders of the Female Genital Tract
Sperm Transport, Fertilization, & Implantation

- The female genital tract is not just a conduit
  - facilitates sperm transport
  - cervical mucus traps the coagulated ejaculate
  - the fallopian tube picks up the egg
- Fertilization must occur in the proximal portion of the tube
  - the fertilized oocyte cleaves and forms a zygote
  - enters the endometrial cavity at 3 to 5 days
- Implants into the secretory endometrium for growth and development

Congenital Anatomic Abnormalities





Unexplained infertility

- 10% of infertile couples will have a completely normal workup
- Pregnancy rates in unexplained infertility
  - no treatment 1.3-4.1%
  - clomid and intrauterine insemination 8.3%

- gonadotropins and intrauterine insemination 17.1%

Summary

- Infertility is the inability to conceive following unprotected sexual intercourse
- Infertility should be evaluated after one year of unprotected intercourse
- Primary infertility - a couple that has never conceived
- Secondary infertility - infertility that occurs after previous pregnancy regardless of outcome
- History and Physical examination usually will help to identify the etiology.

Epilepsy

- Chronic brain disease of diverse etiology
- Characterized by recurrent paroxysmal episodes of uncontrolled excitation of brain neurons
- Manifesting as brief episodes (seizures) of loss of consciousness, with or without characteristic body movements (convulsions)

Status epilepticus (SE)

Continuous convulsion lasting longer than 30 minutes OR Occurrence of serial convulsions between which there is no return of consciousness

Pathophysiology of Epilepsy

- Normally, a balance between excitatory and inhibitory factors - proper functioning of a healthy human brain
- Reduction of inhibitory synaptic activity or enhancement of excitatory synaptic activity -trigger a seizure
- NTs mediating the bulk of synaptic transmission in the mammalian brain are amino acids
- GABA - principal inhibitory
- Glutamate - excitatory neurotransmitters
- Repeated epileptic discharge can cause neuronal death (excitotoxicity).
- A relative deficiency of inhibitory neurotransmitters such as GABA
- An increase in excitatory neurotransmitters such as glutamate would promote abnormal neuronal activity

Clinical manifestations of Epilepsy

- Depend on the location of the focus and the pathways involved in its spread
- 'Generalised' - initial activation of both hemispheres of the brain
- 'Partial' or 'Focal' - discharge starts in a localised area of the brain

Classification of seizure types.

Partial seizures
Simple partial seizures
Complex partial seizures
Partial seizures secondarily generalized
Generalized seizures
Generalized tonic-clonic (grand mal) seizures
Absence (petit mal) seizures
Tonic seizures
Atonic seizures
Clonic and myoclonic seizures
Infantile spasms[1]

[1]An epileptic syndrome rather than a specific seizure type; drugs useful in infantile spasms will be reviewed separately.

Grandmal seizure

- Generalized convulsion, also called the **grand-mal seizure**.
- Patient loses consciousness and usually collapses.
- Followed by generalized body stiffening (called the "tonic" phase of the seizure) for 30 to 60 seconds,
- violent jerking (the "clonic" phase) for 30 to 60 seconds,
- patient goes into a deep sleep.
- During grand-mal seizures, injuries and accidents may occur,
- Tongue biting and urinary incontinence

Absence seizures

- Short loss of consciousness (just a few seconds) with few or no symptoms
- Patient, most often a child

- Seizures begin and end abruptly
- Patients are usually not aware that they are having a seizure, except that they may be aware of "losing time."

Myoclonic seizures

- Consist of sporadic jerks
- Usually on both sides of the body
- Patients sometimes describe the jerks as brief electrical shocks
- When violent, these seizures may result in dropping or involuntarily throwing objects

Clonic seizures

- Repetitive
- Rhythmic jerks
- Involve both sides of the body at the same time

Tonic seizures

Tonic seizures are characterized by stiffening of the muscles.

Atonic seizures

- Sudden and general loss of muscle tone
- Particularly in the arms and legs
- Often results in a fall

Simple partial seizures

- *Key feature is preservation of consciousness*
- A sudden depolarization within a group of neurons called Paroxysmal depolarizing shift (pds)
- Lasts for 200 ms occurs in case of patients with partial seizures.
- This results in generation of an abnormally rapid train of action potentials

Complex partial seizure

- Impaired consciousness lasting 30 seconds to 2 minutes

- Often associated with purposeless movements such as lip smacking or hand wringing
- Associated with amnesia

Secondarily generalized seizure

- Partial seizures may get generalized
- spreading along diffuse connections to involve both cerebral hemispheres
- This seizure spread occurs through several pathways
- U FIBRES connect various regions of the cortex.
- CORPUS CALLOSUM allows for spread between hemispheres.
- THALAMOCORTICAL PROJECTIONS provide a pathway for diffused synchronized spread throughout the brain

Summary

- Epilepsy is characterized by recurrent paroxysmal episodes of uncontrolled excitation of brain neurons
- Manifesting as brief episodes (seizures) of loss of consciousness, with or without characteristic body movements (convulsions)
- Continuous convulsion lasting longer than 30 minutes is status epilepticus

Parkinson's disease

Definition:

A neurological syndrome characterized by tremor, rigidity, hypokinesia and postural instability. As the symptoms progress patient may have difficulty in walking, talking or completing other simple tasks.

Disease is named after the English doctor James Parkinson, who published the first detailed description in "An Essay on the Shaking Palsy" in 1817

"Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with propensity to bend the trunk forward and to pass from walking to a running pace; the senses and the intellects being uninjured."

Parkinsonism

Epidemiology:

- Approximately 15 per 100000 to 90 per 100000 are estimated to suffer from parkinsonism

- Less common in Asian countries
- Risk of developing during one's lifetime 2-3 %
- The 2nd most common neurodegenerative disorder

Etiology & Pathogenesis of Parkinson's disease

Parkinsonism is either idiopathic or secondary

Idiopathic: Denotes a disease of unknown cause

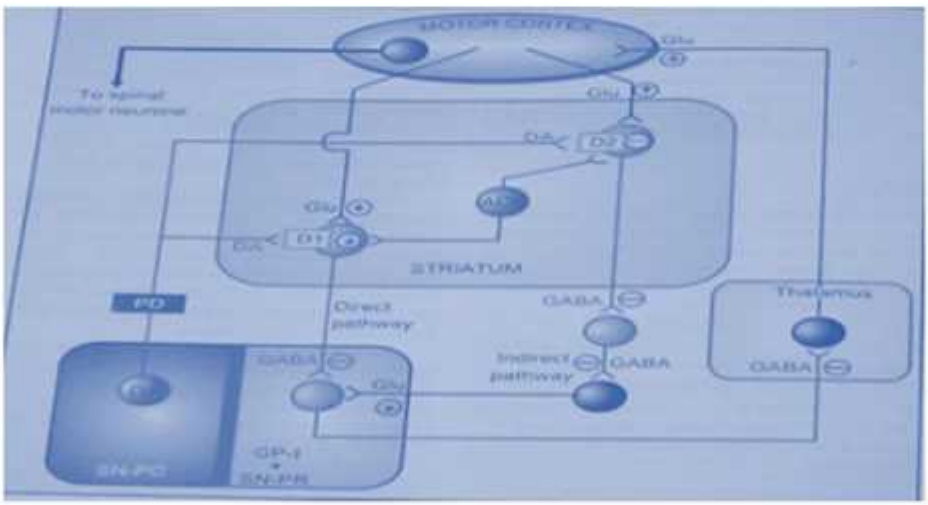
Secondary: Only small amount of cases:

- Trauma induced
- Chemical induced- heavy metals, carbon monoxide, cyanide, pesticides, dyes, methyl chloride
- Drug induced- phenothiazines, reserpine, butyrophenol, large doses of carbamazepine
- Infection induced- syphilis, typhoid, herpes, encephalitis may mimic parkinsonism
- Tumour induced- Intracranial tumour
- Post cephalic- A sequel of the viral infection *Encephalitis lethargica*

Physiology of nigrostriatal pathways

Anatomically, the basal ganglia form a re-entrant loop by

- Receiving the input from the cerebral cortex.
- Processing this information in the context of dopaminergic input from substantia nigra &
- Sending information back to the cortex by way of the thalamus.

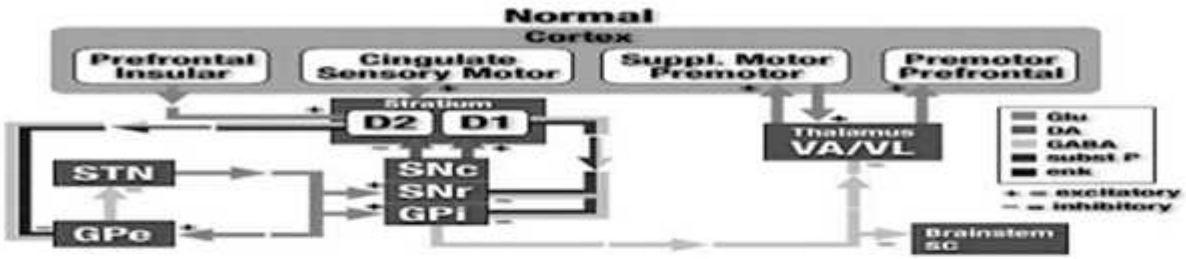


The outflow of striatum proceeds along two distinct routes, identified as direct and indirect pathways, the balance of which regulates the movement.

DIRECT PATHWAY:

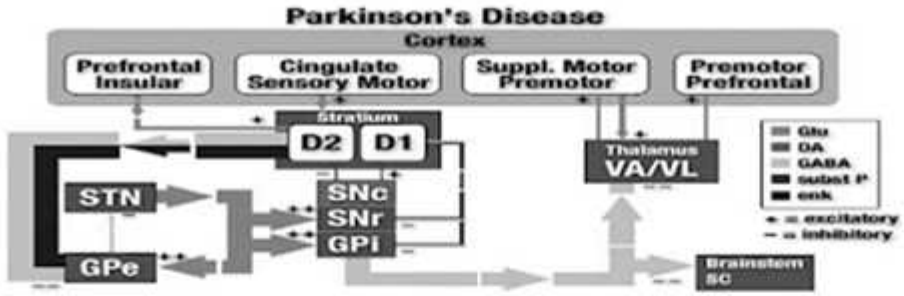
- It is also known as pyrimidal pathway.

- Formed by striatal neurons expressing primarily dopamine D1 receptors.
- These neurons projects directly to the output of the basal ganglia, the internal segment of the globus pallidus.
- These neurons tonically inhibit the thalamus, which in turn, sends excitatory projections to the cortex that initiate movement.



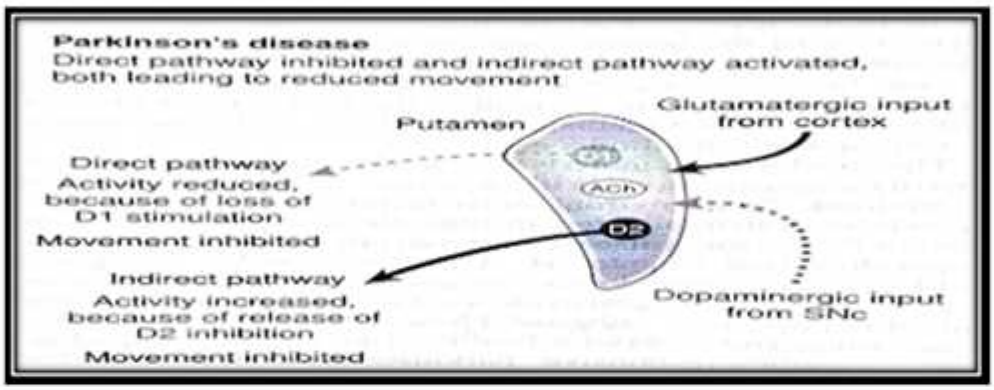
INDIRECT PATHWAY :

- It is also known as extrapyrimidal pathway.
- Formed by the striatal neurons expressing predominantly dopamine D2 receptors.
- These neurons projects to the external segment of the globus pallidus, which in turn inhibits the neurons in the subthalamic nuclei.
- The neurons in the subthalamic nucleus are excitatory glutaminergic neurons that project to the internal segment of the globus pallidus
- The indirect pathway inhibits movement.
- The differential expression of D1 & D2 receptors within the two pathways leads to differing effects of dopaminergic stimulation.
- Increased levels of dopamine in the striatum tend to activate the D1 expressing neurons of the direct pathway while inhibiting the D2 expressing neurons of the indirect pathway. Both of these effects promote movement.
- The opposite effect is seen in PD, a state of dopamine deficiency: the direct pathway shows reduced activity while indirect pathway is overactive, leading to reduced movement.
- In PD, neurons that extend from the substantia nigra to the putamen and caudate nucleus degenerate, causing the disruptions.



- Thus loss of nigrostriatal dopamine neurons in IPD results in reduction of cortical activation.

- Virtually all the motor deficits of IPD are attributable to the marked loss in dopaminergic neurons projecting to the putamen.



- DA has a balance with the excitatory neurotransmitter Ach to initiate motor activities.
- Ach is secreted by cholinergic neurons present in synapses.
- When there is a loss of DA in Parkinsonism, balance is shifted to Ach. Over activity of Ach is responsible for the symptoms of Parkinsonism.

Etiology & Pathogenesis of Parkinson's disease

- Parkinsonism is either idiopathic (primary) or secondary parkinsonism.
- Unlike the idiopathic parkinsonism, many of the secondary forms of parkinsonism can be cured.

Idiopathic Parkinsonism

- The term "idiopathic "denotes a disease of unknown cause.
- Many theories have been proposed & each in succession has been abandoned because of lack of supporting evidence.

  - Neurotoxins highly selective for substantia nigra pars compacta (SNc) dopaminergic neurons –

- 6-hydroxy dopamine
- MPTP(N-methyl 4-phenyl tetrahydropyridine)
- Cellular damage from oxyradicals.
- Dopamine - free radicals from autooxidation and from MAO metabolism

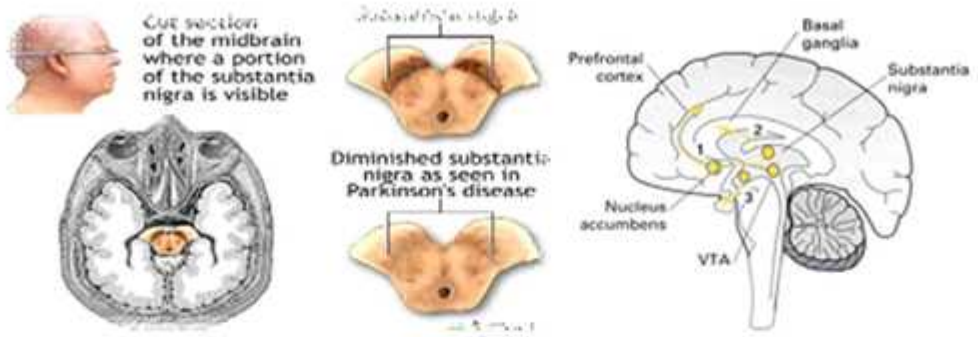
Secondary Parkinsonism

- It is either:
- **Trauma induced-** severe head injuries. They rarely produce Parkinson's symptoms. usually occurs soon after injury & recovery is the general rule
- **Chemical induced-** acute ingestion of large amount of chemicals' such as heavy metals, carbon monoxide, cyanide, pesticides, some photogenic dyes, methyl chloride can produce symptoms of Parkinsonism. But recovery is possible in most cases.
- **Drug induced-** phenothiazines commonly produce extra pyramidal effects that ultimately may manifest as Parkinsonism like syndrome. The true Parkinsonism like syndrome usually appears 2-3 months after initiation of drug therapy. Other drugs besides phenothiazines are haloperidol, butyrophenones, reserpine, large doses of methyl dopa, metochlopramide,carbamazipines.
- **Infection induced-** infection condition like syphilis, typhoid, herpes, coxsakie virus, Japanese encephalitis. Etc may mimic Parkinsonism complication.

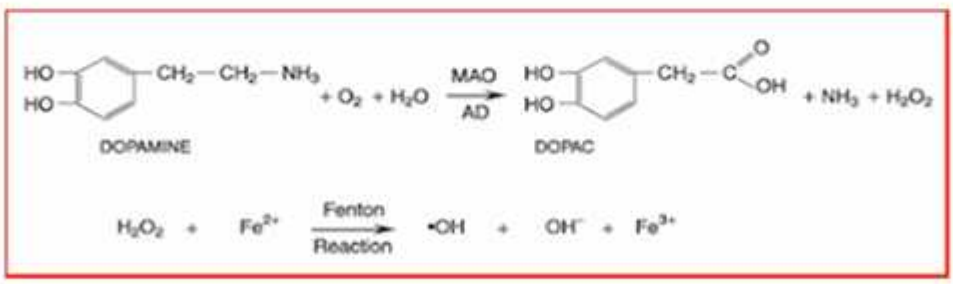
Pathogenesis

- A progressive neurodegenerative disorder
- The pathological hallmark of PD is a loss of the pigmented, dopaminergic neurons of the substantia nigra, with the appearance of intracellular inclusions known as Lewy bodies.
- Caused by degeneration of substantia nigra in the midbrain, and consequent loss of DA-containing neurons in the nigrostrial pathway

- Two balanced systems are important in the extrapyramidal control of motor activity at the level of the corpus striatum and substantia nigra- first neurotransmitter – Ach & the second – D



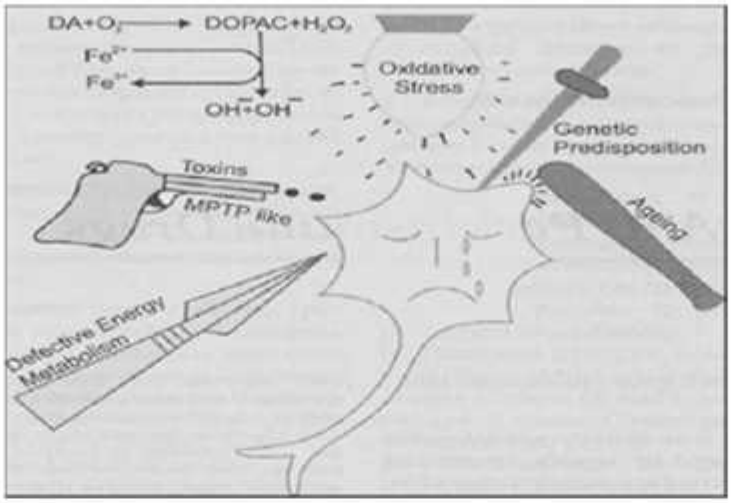
- Neurons which produce the neurotransmitter dopamine in the area of brain substantia nigra die or become impaired resulting in result in loss of DA
- Lewy bodies are the pathological hallmark of the idiopathic disorder
- Dopamine is responsible for transmitting signals b/w substantia nigra to next relay station of brain, the corpus striatum to produce smooth and co-ordinated muscle activity
- The symptoms of PD are connected with loss of nigrostrial neurons and DA depletion
- The cause of selective degeneration of nigrostrial neurones in PD
- is not precisely known, appears to be multifactorial
- Oxidation of DA by MAO-B and aldehyde dehydrogenase generate hydroxyl free radicals (˙OH) in the presence of ferrous iron (basal ganglia are rich in iron)
- Normally these radicals are quenched by glutathione and other endogenous antioxidants
- Age-related (e.g. in atherosclerosis) and/or otherwise acquired defect in protective antioxidant mechanisms allows the free radicals to damage lipid membranes and DNA resulting in neuronal degenerations
- Genetic predisposition may contribute to high vulnerability of substantia nigra neurons
- Environmental toxins or some infections may accentuate these defects
- A synthetic toxin N-methyl-4-phenyl tetrahydropyridine (MPTP), which occurs as a contaminant of some illicit drugs, produces nigrostrial degenerations similar to PD
- Neuroleptics and other DA blockers may cause temporary PD

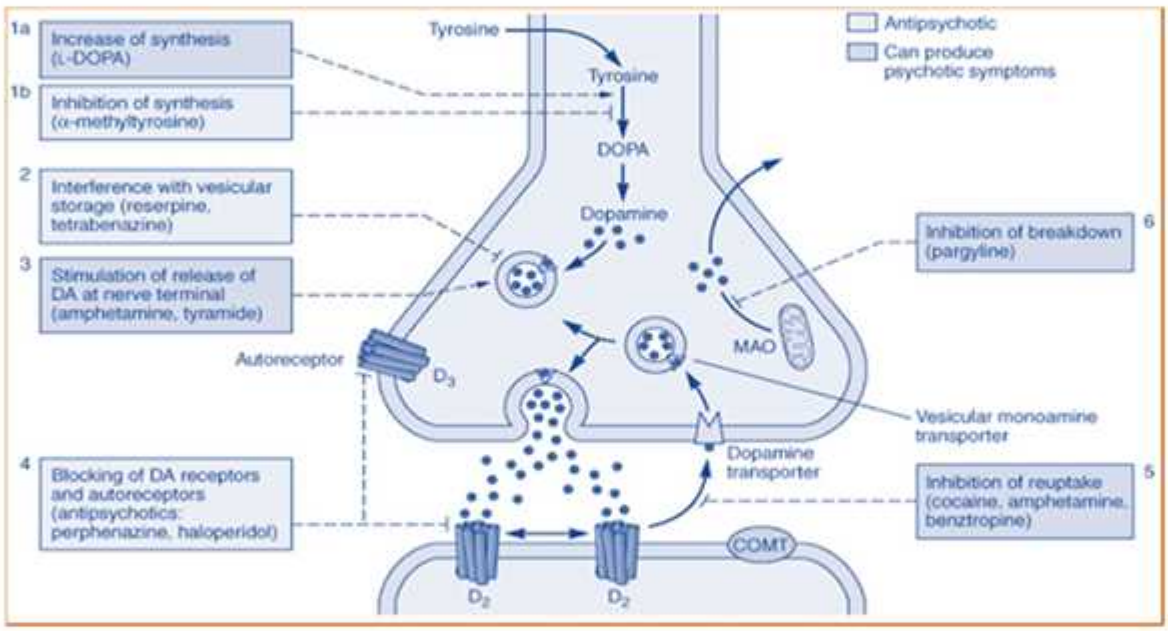


Production of free radical by the metabolism of dopamine (DA)

DA is converted by MAO and aldehyde dehydrogenase (AD) in 3,4-dihydroxyphenylacetic acid (DOPAC), producing hydrogen peroxide (H2O2). In the presence of ferrous ion hydrogen per-oxide undergoes spontaneous conversion, forming a hydroxyl free radical (The Fenton reaction).

Factors contributing to degeneration of nigrostrial DA-ergic neurones causing PD

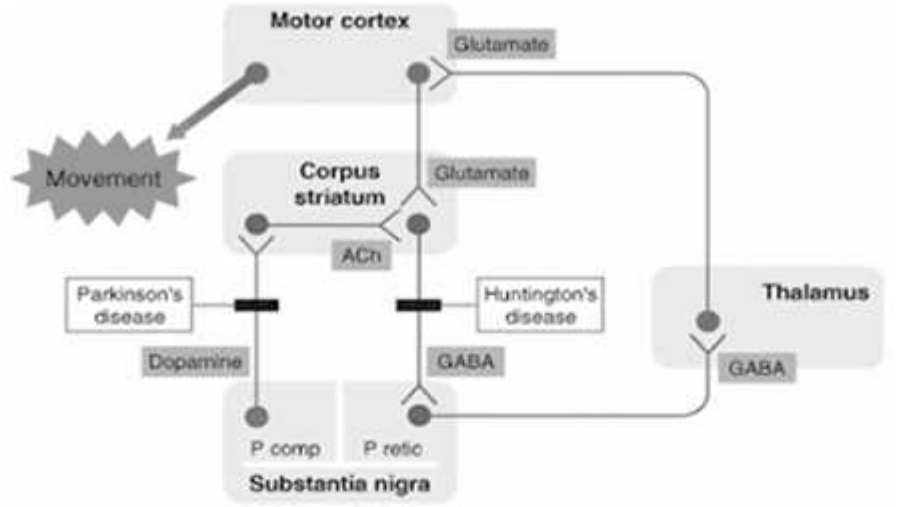


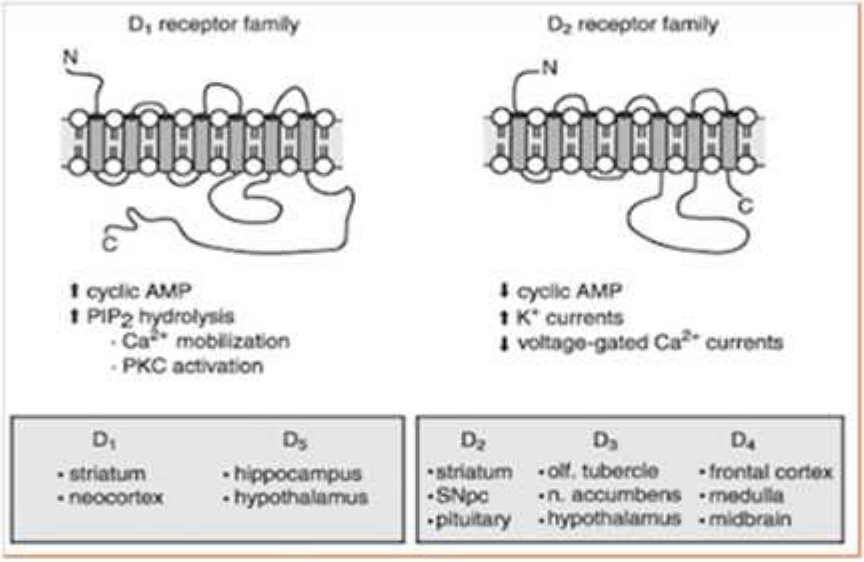


The key steps in the synthesis and degradation of dopamine *and the sites of action of various psychoactive substances at the dopaminergic synapse*

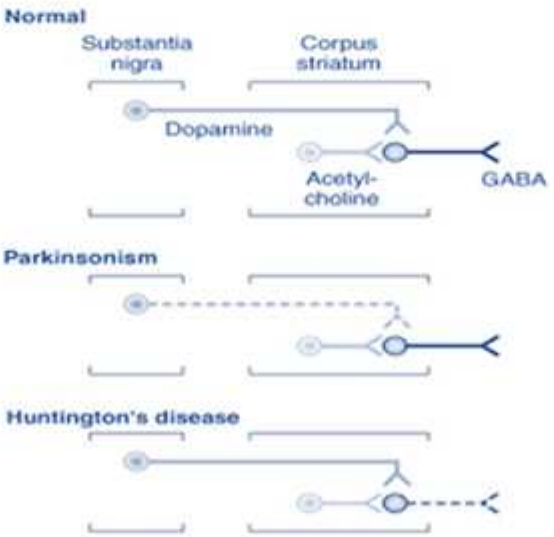
Pathogenesis

- Nerve cells of striatum loose control in co-ordinate muscle activity
- DA has a balance with the excitatory neurotransmitter Ach in the corpus striatum , to initiate motor activities
- When there is a loss of DA in Parkinsonism , balance is shifted to Ach , therefore over activity of Ach is responsible for the symptoms of Parkinsonism.





Distribution and characteristics of DA receptors in the central nervous system



Complications

The disease is often accompanied by these additional problems, which are variably treatable

- Thinking difficulties
- Depression and Emotional changes
- Sleep problems and sleep disorder
- Bladder problems
- Constipation
- Sexual dysfunction

Symptoms of Parkinsonism

The signs of advanced Parkinsonism are so striking and unique that it hardly ever possses a diagnostic challenge.

The symptoms are connected with loss of nigrostrial neurons and DA depletion.

Cardinal Features

- Bradykinesia
- Postural instability
- Resting tremor (may have postural and action components)
- Rigidity

Motor Symptoms

- Decreased dexterity (lack of mental skill or quickness)
- Dysarthria (speech disorder)
- Dysphagia (difficulty in swallowing)
- Festinating gait
- Flexed posture
- “Freezing” at initiation of movement
- Hypomimia- mask like face
- Hypophonia- soft speech
- Micrographia- small cramped hand writing
- Slow turning

- Autonomic Symptoms
- Bladder and anal sphincter disturbances
- Constipation
- Diaphoresis
- Orthostatic blood pressure changes
- Paroxysmal flushing
- Sexual disturbances
- Mental Status Changes
- Bradyphrenia- slowness of thought
- Confusional state
- Dementia
- Psychosis (paranoia, hallucinosis)
- Sleep disturbance
- Fatigability
- Oily skin
- Pedal edema
- Seborrhea (excessive discharge from the sebaceous glands, forming greasy scales on the body)

Treatment

- Primarily at providing maximal relief of symptoms and maintaining the independence and movement
- Successful treatment involves a total program of drug therapy, physical therapy, psychological support, and occasionally surgery

Surgical therapy- Most effective surgical technique is deep brain stimulation (DBS) of the STN, which decreases outflow from this region and reduces input to the thalamus.

Drugs are classified as follows:

- Drugs which increase the dopamine levels

- Anticholinergics
- Anti histamines
- Dopamine agonist

Non Pharmacological Therapy

- Well balanced high fiber diet
- Psychotherapy
- Physical therapy
- Speech therapy

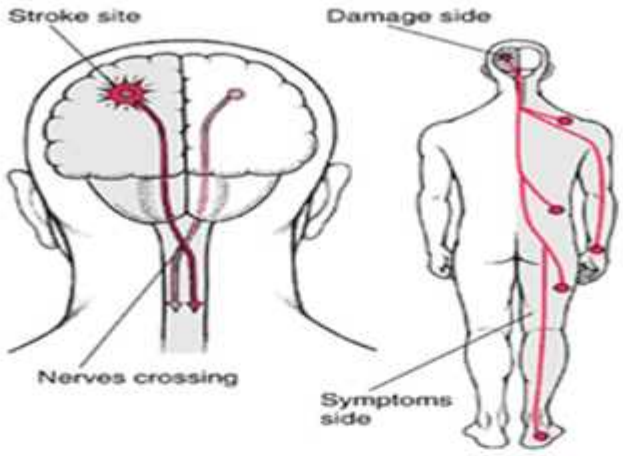
Summary

- Many theories have been proposed & each in succession has been abandoned because of lack of supporting evidence.
  - Neurotoxins highly selective for substantia nigra pars compacta (SNc) dopaminergic neurons –
    - 6-hydroxy dopamine
    - MPTP(N-methyl 4-phenyl tetrahydropyridine)
  - Cellular damage from oxyradicals.
  - Dopamine - free radicals from autooxidation and from MAO metabolism
- Cardinal Features of PD: Bradykinesia, Postural instability, Resting tremor (may have postural and action components), Rigidity

Stroke

What is STROKE?

- Sudden brain damage
- A stroke occurs when a blood clot blocks a blood vessel or artery, or when a blood vessel breaks, interrupting blood flow to an area of the brain
- Lack of blood flow to the brain caused by a clot or rupture of a blood vessel



Strokes occur in the brain and affect the opposite side of the body

National Stroke Association encourages everyone to spread awareness about stroke in May about how to:

- **STOP** primary and secondary stroke through risk factor management

- **Act F.A.S.T.** to increase recognition of and response to stroke symptoms

- **Spread HOPE** about recovery from stroke

May is National Stroke Awareness Month

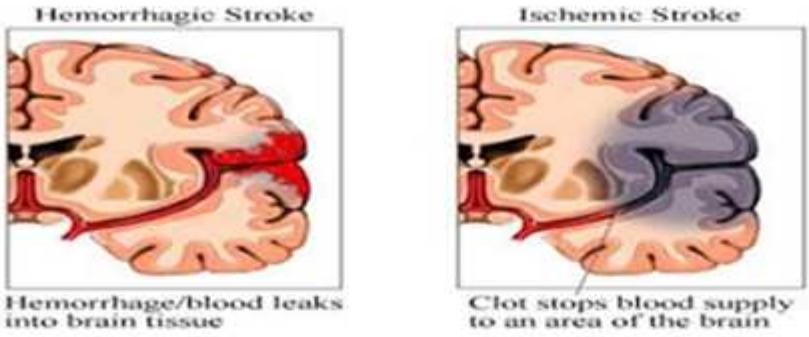
STROKE FACTS

- A leading cause of death in the United States
- 795,000 Americans suffer strokes each year
- 134,000 deaths each year
- From 1996 to 2006, the stroke death rate fell 33.5% and number of deaths fell by 18.4%
- A leading cause of adult disability
- Up to 80% of all strokes are preventable through risk factor management

Types of Strok

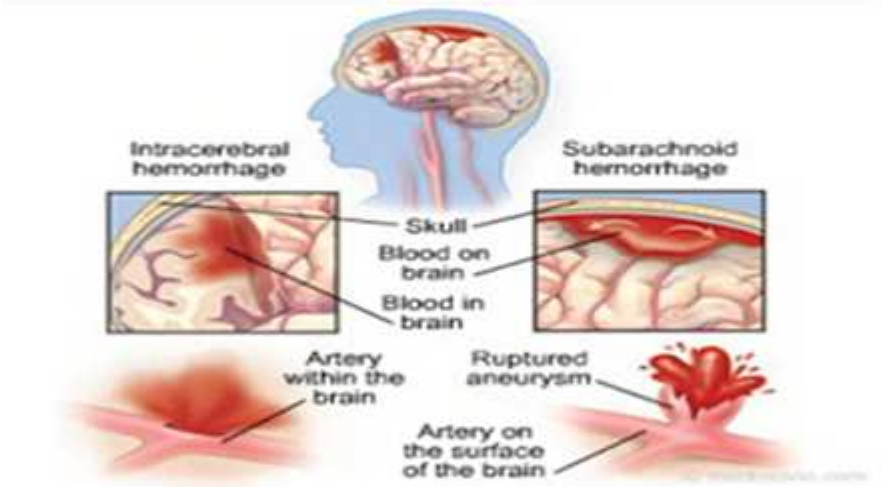
Hemorrhagic Stroke

Ischemic Stroke



HEMORRHAGIC STROKE

- Hemorrhagic Stroke is a type of stroke which occurs when a blood vessel in the brain breaks or ruptures
- Approximately 20% of the strokes are hemorrhagic in nature
- Most leading cause is high blood pressure occurring when a blood vessel bursts and blood accumulates



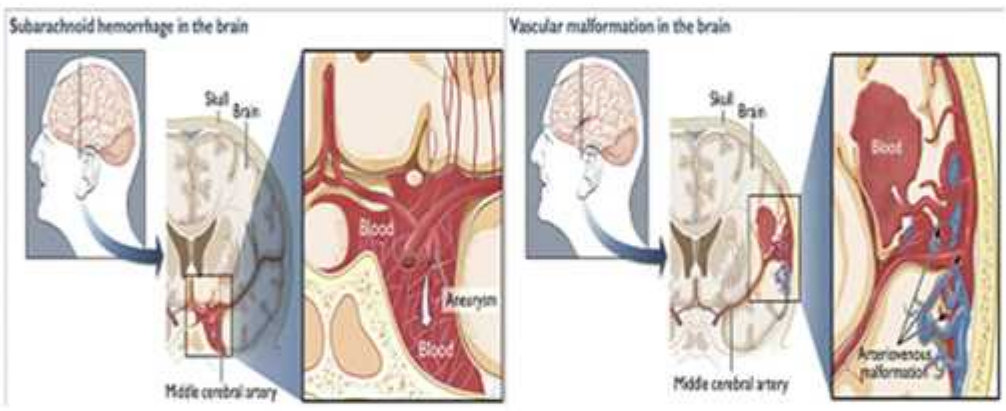
- Two types of Hemorrhagic strokes:
  - Subarachnoid hemorrhage and
  - Intracerebral hemorrhage

ETIOLOGY:

- Traumatic head injury
- Burst of cerebral aneurysm
- A defect of the circulatory system/a cluster of abnormally formed blood vessels (also called arteriovenous malformation or AVMs, usually inherited at birth)

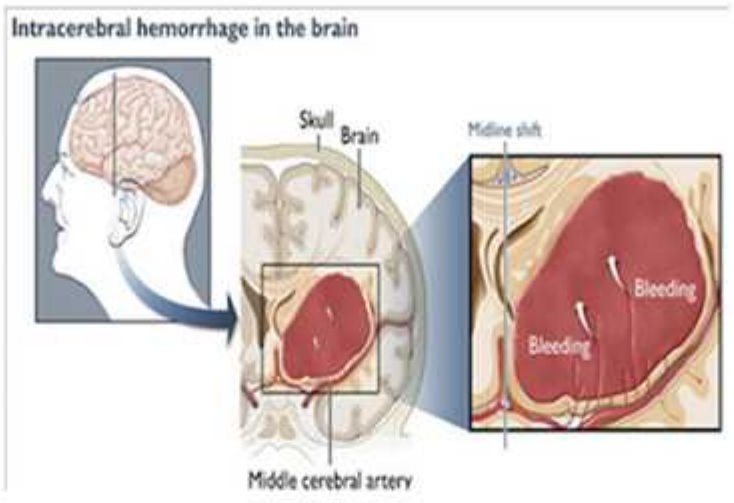
1. Subarachnoid Hemorrhage

- Subarachnoid hemorrhage - most severe form of a stroke - permanent disability or death
- It can happen suddenly when a major blood vessel bursts upon the surface of the brain causing spilling blood into the cerebrospinal fluid surrounding the brain
- Due to bleeding, the amount of fluid increases in the affected area - enormous pressure on the whole brain - damage to the brain tissue
- Aneurysm is a ballooning of a weakened area of an artery and when left untreated the aneurysm can continuously become weakened until it ruptures and finally bleeds into the brain
- Burst aneurysm can lead to a sudden and severe headache, usually with a description of "thunderclap"
- CT scan or an MRI - detect the presence of subarachnoid hemorrhage



Intracerebral hemorrhage

- Intracerebral hemorrhage happens when there is a burst of a blood vessel in the brain - leaking of blood into the brain
- It is more common among people aged above 60 and can be most commonly caused by high blood pressure
- It can also be a result of infections, a burst aneurysm tumors or head injuries



ISCHEMIC STROKE

- Ischemic stroke is a sudden loss of brain function and can be caused by partial or complete obstruction of a blood vessel supplying the brain

- Approximately 80% of strokes are ischemic in nature, and it occurs when there is a blockage inside the carotid arteries or in the vertebral arteries

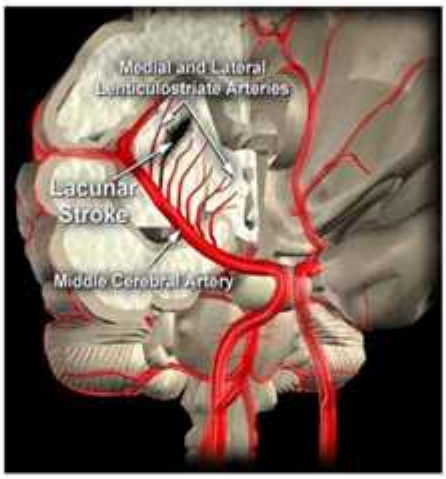
- A fatty deposit (a plaque) or mass of blood cells (a clot) travelling in the blood can get trapped in a narrowed or small artery - obstruct blood flow - occurrence of a stroke

There are three types of Ischemic stroke:

1. Lacunar stroke
2. Thrombotic stroke
3. Embolic stroke

1. Lacunar stroke:

- Lacunar stoke contributes to 25% of ischemic strokes and occurs when there is a blockage in one of the smaller blood vessels found inside the brain
- A “hole” of scar tissue is due to the blockage that starves a small part of the brain
- As only small portion of the brain is affected, lacunar stroke is usually hard to be diagnosed



2. Thrombotic stroke:

- It happens when the artery is clogged by plaque and hardens, or when a cholesterol-filled plaque of atherosclerosis especially in a brain (cerebral), carotid or vertebral artery breaks open - formation of a blood clot over the plaque obstructing blood flow
- Thrombus (blood clot) is a condition where the blockage seals off the blood vessel

3. Embolic Stroke:

- An embolus refers to a piece that breaks off and can block a blood vessel supplying the brain causing the occurrence of an embolic stroke which contributes 60% of ischemic strokes
- Unless the source is found and treated immediately, people with embolic strokes are at potential risk of another stroke/s
- Embolic strokes hit fast and sudden and are normally severe

RISK FACTORS OF STROKE

1. High blood pressure is the number one risk factor for strokes.
2. Atrial fibrillation
3. Diabetes mellitus
4. Family history of stroke
5. High cholesterol

6. Increasing age, especially after age 55
7. Race (black people are more likely to die of a stroke)
8. People who have heart disease or poor blood flow in their legs caused by narrowed arteries
9. Being overweight or obese
10. Drinking heavily
11. Eating too much fat or salt
12. Smoking
13. Taking cocaine and other illegal drugs
14. Birth control pills can increase the chances of having blood clots. The risk is highest in woman who smoke and are older than 35

Signs & Symptoms

Sudden and severe headache

Trouble seeing in one or both eyes

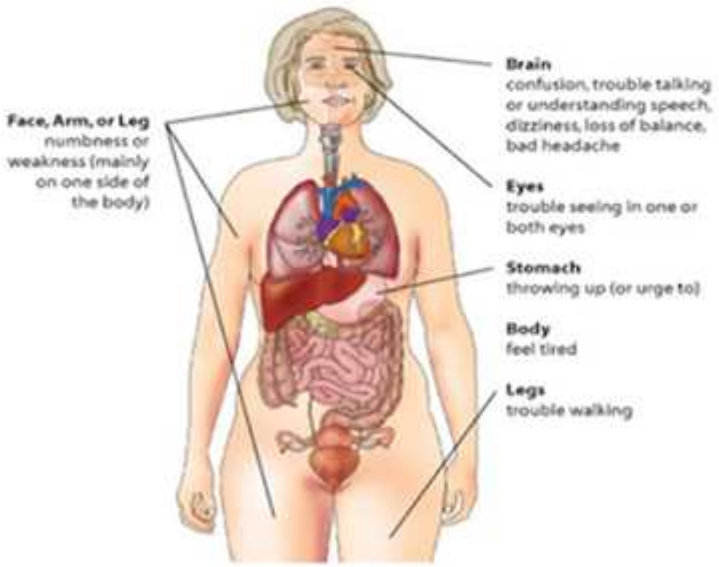
Sudden dizziness

Trouble walking

Sudden confusion

Trouble speaking

Sudden numbness or weakness of face, arm or leg



RECOGNIZE THE SYMPTOMS OF A STROKE

- 3 Simple Questions
  - Ask the person to smile

- Ask the person to raise both arms
- Ask the person to say a simple sentence “The sky is blue ”

Diagnosis

- **Diagnostic Testing**
  - CT or MRI of the brain
  - EKG
  - Carotid Ultrasound
  - Echocardiogram

Summary

- stroke occurs when a blood clot blocks a blood vessel or artery, or when a blood vessel breaks, interrupting blood flow to an area of the brain
- Hemorrhagic stroke occurs as a result of traumatic head injury, burst of cerebral aneurysm a defect of the circulatory system/a cluster of abnormally formed blood vessels
- Ischemic stroke occurs due to sudden loss of brain function and can be caused by partial or complete obstruction of a blood vessel supplying the brain by atherosclerotic plaque

Depression

Depression is a state of low mood and aversion that can affect a persons’s thoughts, behavior, feelings, and sense of well being

Causes of Depression

- **Family History**
  - Having a family members who have depression may increase a person’s risk
  - Imbalances of certain chemicals in the brain may lead to depression
- **Major Life Changes**
  - Positive or negative events can trigger depression. Examples include the death of a loved one or a promotion
  - Major Illnesses such as heart attack, stroke or cancer may trigger depression

- Certain medications used alone or in combination can cause side effects much like the symptoms of depression
- Use of Alcohol or other Drugs can lead to or worsen depression
- Depression can also occur for no apparent reason!

Types of depression

- **Major depression**
  - Inability to enjoy life and experience pleasure
  - Symptoms are constant, ranging from moderate to severe
  - Some people experience just a single depressive episode in their lifetime, but more commonly, major depression is a recurring disorder
- **Atypical Depression**
  - Specific symptom pattern, including a temporary mood lift in response to positive events
  - Other symptoms include weight gain, increased appetite, sleeping excessively, a heavy feeling in the arms and legs
  - Atypical depression responds better to some therapies and medications than others
- **Bipolar disorder**

  People with this type of illness change back and forth between periods of depression and periods of mania (an extreme high)
- **Symptoms of mania may include:**
  - Less need for sleep
  - Overconfidence
  - Racing thoughts
  - Reckless behavior
  - Increased energy
  - Mood changes are usually gradual, but can be sudden
- **Season affective disorder**

This is a depression that results from changes in the season. Most cases begin in the fall or winter, or when there is a decrease in sunlight

Depression Pathophysiology

- Biogenic amine hypothesis: Decreased brain levels of the neurotransmitters norepinephrine (NE), serotonin (5-HT), and dopamine (DA)
- Postsynaptic changes in receptor sensitivity: Changes in sensitivity of NE or 5-HT_2 receptors may relate to its onset
- Dysregulation hypothesis: A failure of homeostatic regulation of neurotransmitter systems, rather than absolute increases or decreases in their activities

Symptoms of depression

- Vary from person to person
- 2 key signs - loss of interest in things you like to do and sadness or irritability

Additional signs of depression

- Feeling empty
- Inability to enjoy anything
- Hopelessness
- Loss of sexual desire
- Loss of warm feelings for family or friends
- Feelings of self-blame or guilt
- Loss of self esteem
- Inexplicable crying spells, sadness or irritability

- **Changes in behavior and attitude**

These may include:

- General slowing down
- Neglect of responsibilities and appearance
- Poor memory

- Inability to concentrate
- Suicidal thoughts, feelings or behaviors
- Difficulty making decisions

Physical complaints

- Sleep disturbances such as early morning waking, sleeping too much or insomnia
- Lack of energy
- Loss of appetite
- Weight loss or gain
- Unexplained headaches or backaches
- Stomachaches, indigestion or changes in bowel habits

Summary

- Depression is a state of low mood and aversion that can affect a person's thoughts, behavior, feelings, and sense of well being
- Etiology: family history, major life changes, drugs, work
- Decreased brain levels of the neurotransmitters norepinephrine (NE), serotonin (5-HT), and dopamine (DA), changes in sensitivity of NE or 5-HT_2 receptors - failure of homeostatic regulation of neurotransmitter systems, rather than absolute increases or decreases in their activities

Schizophrenia

Psychotic disorder

Severe mental disorder in which thinking and emotion are so impaired that the individual is seriously out of contact with reality

Disturbance that last for at least 6 months or longer including 1 month of delusions, hallucination, disorganized speech, behavior or negative symptom

Types of Schizophrenia

Paranoid Schizophrenia

- Small delusions & hallucination

Dis organised/ Hebphrenic schizophrenia

- Confused & disorganized pattern of speech, thought & behavior

Catatonic schizophrenia

- Abnormal posture & movement

Undifferentiated schizophrenia

Residual schizophrenia

- No severity of symptoms

Symptoms in Schizophrenia

- **Positive symptoms**

  Excesses / bizarre additions to normal thoughts, emotions or behaviors

- **Negative symptoms**

  Deficits in normal thoughts, emotions, or behaviors

- **Cognitive dysfunction**

  Abnormalities in attention, working memory and executive function

Positive Symptoms

- Distortions or excesses of normal functioning
  - Delusions
  - Hallucinations
  - Disorganized thinking and speech
  - Inappropriate affect
- Positive symptoms are generally more responsive to treatment than negative symptoms

Negative Symptoms

- Introvert behaviour
- Thought disorder with irrational conclusion

- Garbled sentences
- Lack of motivation
- Poor socialization
- Emotional blunting

Types of Negative Symptoms

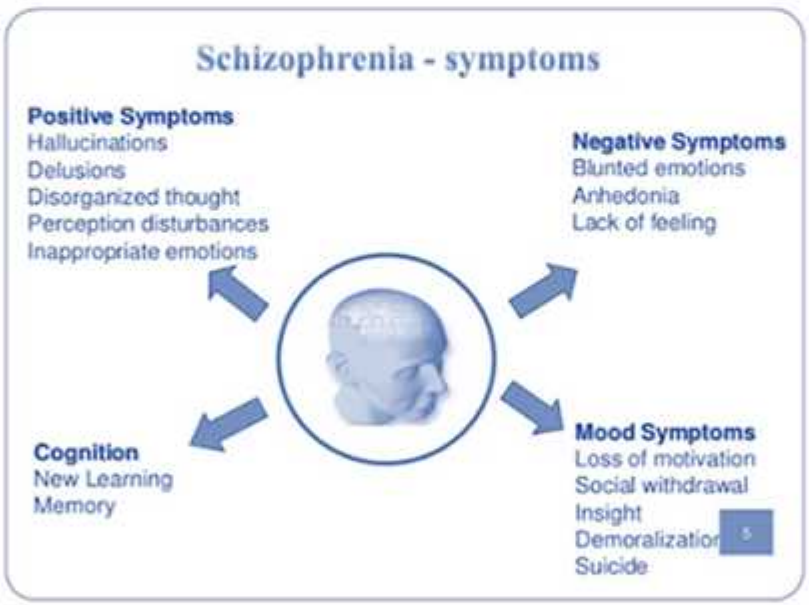
• Poverty of speech or ***Alogia***

• Blunted and flat affect or ***Flat affect***

• Loss of volition or ***Avolition***

• Social withdrawal or ***Anhedonia***

• Psychomotor symptoms or ***Catatonia***



Etiology of Schizophrenia

- Genetics
- Imbalance of neurotransmitter in brain
- Brain damage
- Environmental influence
- Viral attack

Pathogenesis of Schizophrenia

- From dopaminergic symptoms
- Dopamine – inhibitory NT
- Precursor for adrenaline & NA
- Dopamine pathway involved in schizophrenia
  - Mesolimbic dopamine pathway
  - Mesocortic pathway
  - Nigrastriatal pathway
- Increased activity of nigrostriatal region & mesolimbic
- Decreased activity of mesocortical tract
- Overfiring of neurons
- Hallucinations
- Serotonergic pathway also involved

Summary

- Severe mental disorder in which thinking and emotion are so impaired that the individual is seriously out of contact with reality
- Symptoms of schizophrenia are categorized as primary, secondary and cognitive dysfunction
- Pathogenesis of schizophrenia is due to the imbalance and over excitation of certain NT

Alzheimer's disease

- Alzheimer's disease (AD), first characterized by Alois Alzheimera, a German psychiatrist and neuropathologist in 1907 and is a gradually progressive dementia affecting both cognition and behavior
- 'Also known as Senile Dementia of the Alzheimer Type (SDAT)
- A slowly progressive disease of the brain that is characterized by impairment of memory and eventually by disturbances in reasoning, planning, language, and perception
- Many scientists believe AD results from an increase in the production or accumulation of a specific protein (beta-amyloid protein) in the brain leading to nerve cell death

Epidemiology of Alzheimer's disease:

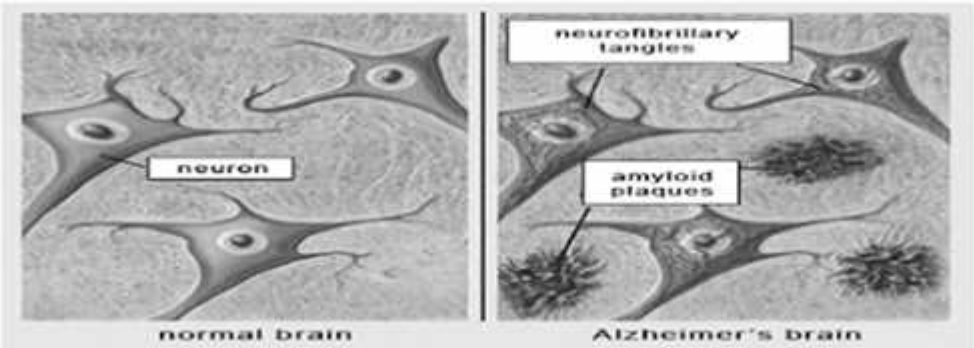
- Disease responsible for 55% of the total causes of dementia
- Survival following AD onset estimated to be 3 to 20 years, with an average of 8 years
- Known to have affected 35.8 million people in the world and this number is expected to increase by 1/4th by 2050
- The most prevalent cause of deaths in adults after heart disease, cancer and stroke

Etiology of Alzheimer's disease

- Although dementia syndrome may be caused by 60 other disorders, most cases are due to Alzheimer's followed by multi infarct dementia or combination of both
- The putative risk factors for the Alzheimer's dementia include advancing age, a history of serious head trauma, hypothyroidism, dementia in a first circle relative and down's syndrome in a first circle relative
- Alzheimer's disease is correlated with diminished neuron function and decreased neurotransmitters
- The major abnormality observed in the Alzheimer's is a 40-90% decrease in the enzyme choline acetyl esterase in the cerebral cortex and the hippocampus
- Although acetylcholine is the major neurotransmitter deficit associated, other neurotransmitters like somatostatin and corticotrophin-releasing factors are also found to be decreased

Pathogenesis of Alzheimer's disease

- Brain autopsy studies revealed that Alzheimer's patients have cortical atrophy, a significant loss of neurons, an increase in the **neuritic plaques** and a high density of **neurofibrillary tangles**.



Neuropathologically AD destroys neurons in the cortex and limbic areas of the brain such as:

- The basal forebrain, amygdala, hippocampus, and cerebral cortex

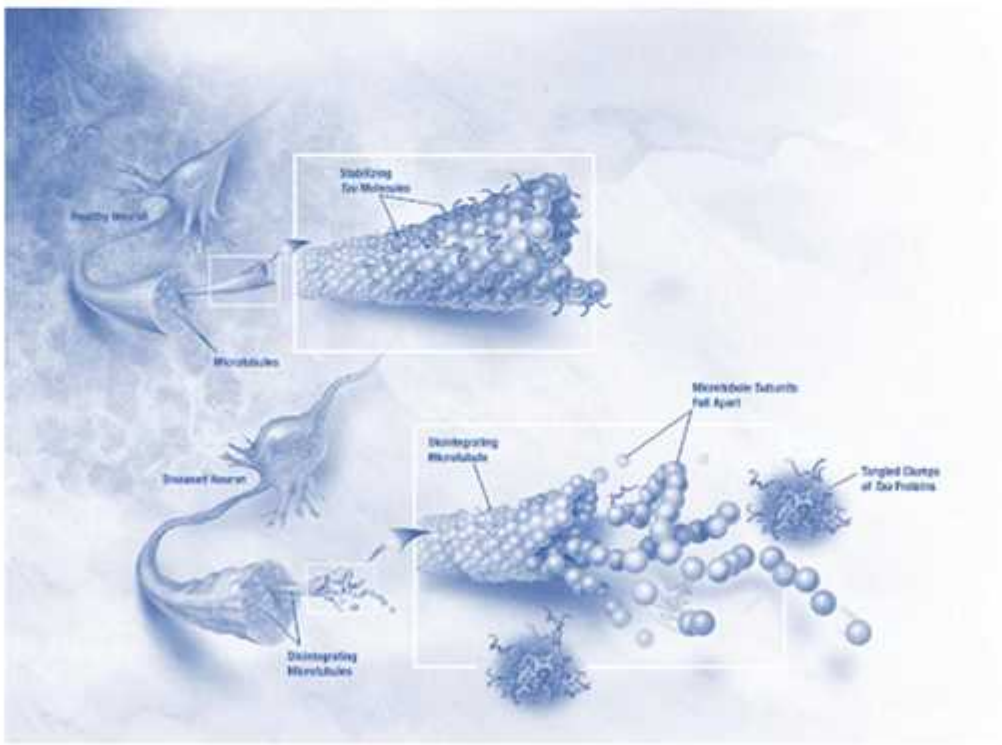
- These areas are responsible for higher learning, memory, reasoning, behaviour, and emotional control

Anatomically, four major alterations in brain structure are seen:

- Cortical atrophy, degeneration of cholinergic and other neurons, presence of neurofibrillary tangles (NFTs), and the accumulation of neuritic plaques
- The signature lesions of AD are NFTs and neuritic plaques

Neuro fibrillary Tangles

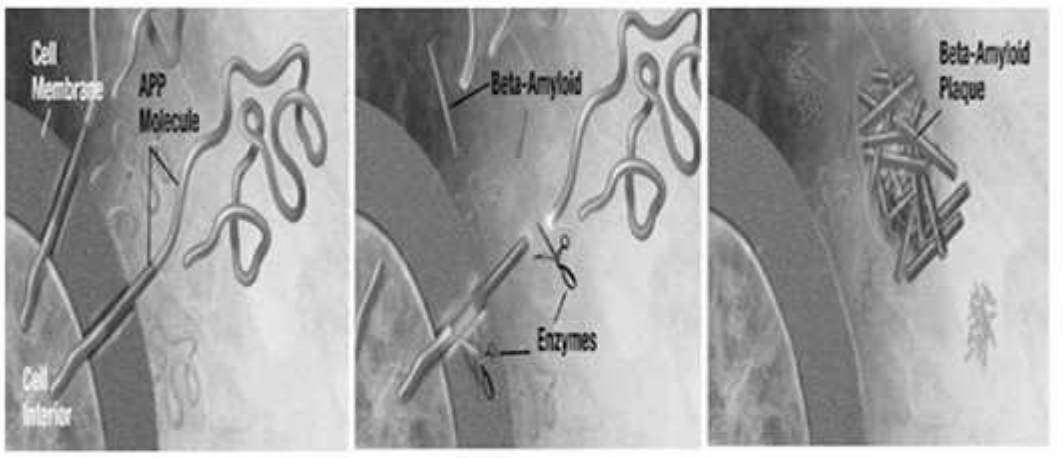
- Aggregates of hyper phosphorylated tau protein
- Tau protein provides structural support to microtubules
- Aggregations of hyper phosphorylated tau protein are also referred to as PHF, or "paired helical filaments
- When tau filaments undergo abnormal phosphorylation at a specific site, they cannot bind effectively to microtubules, and the microtubules collapse
- Without an intact system of microtubules, the cell cannot function properly and eventually dies



Neuritic plaques

- Extracellular deposits of beta amyloid (a 39- to 43-amino acid protein segment) in the gray matter of the brain

- Primarily composed of beta amyloid peptides and an entwined mass of broken neurites (axon and dendrite projections of neurons)
- These polypeptides tend to aggregate and are neurotoxic
- Plaques are variable in shape and size, but are on average 50 μm in size
- Accumulation of aggregated amyloid fibrils disrupts the cell's calcium ion homeostasis and utilization of glucose by neurons inducing apoptosis
- The βAP also accumulate in the brain and cerebral blood vessels
- Two types of glial cells, astrocytes and microglia, also found in plaques
- Glial cells also secrete inflammatory mediators and serve as scavenger cells, which may be important in causing the inflammatory processes that occur in the development of AD



- Enzymes act on the APP (amyloid precursor protein) and cut it into fragments
- The beta-amyloid fragment is crucial in the formation of senile plaques in AD
- **Inflammatory Mediators-** increased presence of APP (Amyloid Precursor Protein), α1-antichromotrypsin and α2-macroglobulin, in the serum and within amyloid plaques of patients with AD has been proved
- α1-antichromotrypsin and α2-macroglobulin act as protease inhibitors affecting proteolytic breakdown of βAP
- Inflammatory mediators increase βAP toxicity and aggregation
- The complement-derived Membrane Attack Complex, is found associated with broken neurites and areas containing NFTs

The cholinergic system-

- Damage occurs in any nerve cell population located in or traveling through plaque laden areas
- Cholinergic neurons located at the base of the forebrain in the nucleus basalis of Meynert, a brain area involved in thought integration is profoundly damaged
- Axons of these cholinergic neurons project to the frontal cortex and hippocampus, areas strongly associated with memory and cognition

Other neurotransmitter abnormalities-

- Serotonergic neurons of the raphe nuclei and noradrenergic cells of the locus ceruleus are lost
- Mao B activity is increased
- Abnormalities appear in glutamate pathways of the cortex and limbic structures (If glutamate is allowed to remain in the synapse for extended periods of time, it can destroy nerve cells)

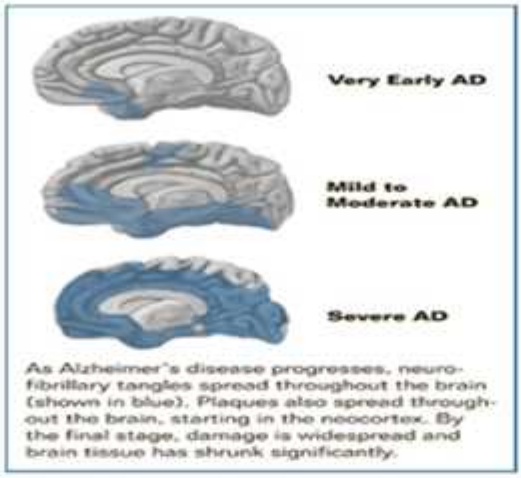
Estrogen-

- Promotes neuronal growth, prevents oxidative damage, benefiting cells exposed to βAP
- Important in maintaining normal cholinergic neurotransmission
- Estrogen receptors are present in the hippocampus, cerebral cortex, and basal forebrain
- Estrogen receptors colocalize with receptors for nerve growth factor on cholinergic nerve terminals
- Estrogen supplementation also prevents decrements in choline uptake and choline acetyltransferase concentrations
- Thus estrogen is important in maintaining normal cholinergic neurotransmission
- May also increase NMDA receptor numbers in brain areas involved in recording new memories
- Prevents cell damage by acting as an antioxidant

Role of Apo lipo protein E and cholesterol

- Current research reveals the role for Apo lipo protein E(Apo E) in the pathogenesis of Alzheimer's disease
- Apo E binds to the β-amyloid in the neurotic plaques and tangles
- Identification of this ApoE4 allele may eventually be used as a diagnostic aid or may be used for pre-symptomatic testing for the Alzheimer's disease
- Cholesterol depletion can inhibit the amyloidogenic pathway and prevent or slow down the plaque formation process

Stages of Alzheimer's disease:



Symptoms of developing Alzheimer's disease

Early stage:

- A mild/early stage with duration period 2-4 years
- Frequent recent memory loss, particularly of recent conversations and events
- Repeated questions, some problems expressing and understanding language
- Writing and using objects become difficult and depression and apathy occur
- Drastic personality changes may accompany functional decline
- Need reminders for daily activities and difficulties with sequencing impact driving early in this stage

Second stage:

- Memory impairment progresses and early deficits of the early stage becomes more pronounced
- Decreased performance in the demanding employment or social situations
- Blunting of emotions and apathy common
- Judgement, the capacity for abstract thinking and calculations begin to wane or are lost
- Patients have difficulty in finding words and names
- Prevalence of agitation which can be aggressive/non-aggressive, physical or verbal, can increase with disease progression
- Psychotic symptoms like hallucinations, delusions and paranoia more become more prevalent towards the end of this stage

- Patients often become disoriented, lost, or wander and independent living becomes hazardous

Final stage:

- There is disturbance of practically all intellectual functions
- Patients are disoriented and incapacitated
- Activities of daily living is so impaired that independent living becomes hazardous
- Marked neurologic deficits and often increased muscle tone, akinesia, resulting in a slow and unsteady gait
- Loss of former personality traits
- Patients often fail to recognize relatives or even forget their own names
- Eventually become bedfast, become incontinent of the bowel and bladder
- Death is usually the result of pneumonia or other infections

Diagnosis of Alzheimer's disease

- Usually diagnosed clinically from the patient history, collateral history from relatives, and clinical observations, based on the presence of characteristic neurological and neuropsychological features and the absence of alternative conditions
- CT or MRI
- Positron Emission Tomography (PET)
- Neuropsychological tests such as the mini-mental state examination (MMSE) are widely used to evaluate the cognitive impairments needed for diagnosis.
- Psychological tests for depression are employed, since depression can either be concurrent with AD, an early sign of cognitive impairment, or even the cause

Treatment of Alzheimer's disease

- Two basic divisions of the Alzheimer's drug treatment

1. First division and most often used is *symptomatic* drugs that are palliative and help to control unwanted behaviours and maintain patient's normal functioning. These drugs primarily consist of psychotropic agents.
2. The other division is *therapeutic drugs.* These agents are used to stop or reverse the disease process and are largely experimental.

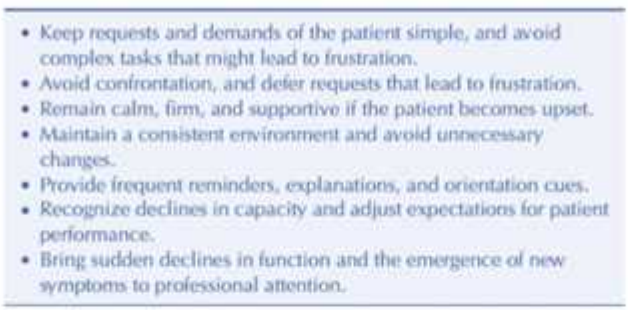
Primary goal

- To symptomatically treat cognitive difficulties and preserve patient function as long as possible

Secondary goal

- Treating the psychiatric and behavioral sequelae that occur as a result of the disease

Nonpharmacologic Therapy/ Basic Principles of Care for the Alzheimer's Patient



- Keep requests and demands of the patient simple, and avoid complex tasks that might lead to frustration.
- Avoid confrontation, and defer requests that lead to frustration.
- Remain calm, firm, and supportive if the patient becomes upset.
- Maintain a consistent environment and avoid unnecessary changes.
- Provide frequent reminders, explanations, and orientation cues.
- Recognize declines in capacity and adjust expectations for patient performance.
- Bring sudden declines in function and the emergence of new symptoms to professional attention.

Symptomatic Treatment of Alzheimer's disease

1. Antidepressants:

- Early stages of Alzheimer's often accompanied by depressive symptoms which may respond to drug therapy
- Resolution of the depression results in improvement of mood, functional abilities, and possibly cognitive functions
- All patients with dementia should be carefully evaluated for depression
- Depressive symptoms such as agitation, memory loss and insomnia can be easily confused with dementia
- Tricyclic antidepressants
- Newer Serotonin Specific Reuptake Inhibitors
- Atypical antidepressants
- For depressed Alzheimer's patients who do not respond to tricyclics, SSRIs and other standard antidepressants or those who suffer from troublesome side effects the use of MAOIs should be considered

Classification of anti-depressants:

A) Monoamine oxidase inhibitors:

e.g. Hydrazines, Phenelzine, Clorgiline, selegiline, meclobemide

MOA:

- MAOI increase the concentration of NE, 5HT, DA within the normal synapse through inhibition of the MAO enzyme.

- Chronic therapy of MAOI causes changes in receptor sensitivity.

Drug interaction:

- Cheese
- Cold cough remedies
- Reserpine and levodopa.

These are metabolized in liver and excreted through urine.

Adverse effect:

- Fatigue
- Irritability
- tremor
- Insomnia
- Headache
- Dizziness
- Weight gain
- Blurred vision
- constipation

B) Tricyclic's:

i. Noradrenaline and serotonin reuptake inhibitors**:** these inhibit the re uptake of NA, and 5HT- **e.g.** Imipramine, Amitrptyline, Doxepine, clomipramine

ii. Noradrenaline re uptake inhibitor: Inhibits the reuptake of NA.

e.g. Nortyptyline, protryptiline, Amoxapine

iii. Selective serotonin re uptake inhibitors: Fluoxetine, paroxetine, Fluvoxamine

iv. Atypical anti-depressants: Trazadone, Bupropion, Mianserin, Nefazodone

Adverse effects

- Dry mouth
- Bad taste
- Constipation

- Epigastric distress
- Palpitation
- Blurred vision
- Sedation
- weakness

2. Hypnotics

- Insomnia is a common complaint among the elderly and it is even more prevalent in demented patients
- Sleep disturbances can be manifested by patients being awake at night, trying to go outside, or searching for lost items
- At such times hypnotics are given
- Sedating antidepressants trazadone 25 to 50mg at bedtime may be beneficial
- The short acting benzodiazepines triazolam, temazepam and zolpidem are often helpful
- Should be judiciously used because they can increase confusion and memory impairment, worsen depressive symptoms and aggrevate most other cognitive functions related to Alzheimer's
- Chloral hydrate has been used in low doses
- Has many side effects too and more drug interactions than benzodiazepines, caution has to be taken because this drug can exacerbate symptoms of Alzheimer's
- Diphenhydramine, used for its moderate sedating properties but has anticholinergic effects that may increase confusion and psychotic symptoms
- Alcohol intake has to be stopped or kept at very minimum level because of its effects on cognition, disruption of sleep pattern and other side effects

3. Anxiolytics

- Anxiety frequently affects patients with memory loss
- Judicious use of benzodiazeoines and buspirone in treating these symptoms has been successful
- Buspirone effective for the anxiety and mild agitation of the Alzheimer's disease and has minimal side effects

4. Neuroleptics

- Indicated for specific psychotic symptoms such as auditory and visual hallucination, paranoia, and delusions with suspiciousness and severe agitation, which are stressful for the patients
- Do not affect higher cortical functions such as memory, judgement, and problem solving
- High potency anti-psychotics (haloperidol, fluphenazine) leave the patient prone to extrapyramidal side effects such as parkinsonism and tardive dyskinesia
- Low potency (chlorpromazine, thioridazine) are anti cholinergic and have cardiovascular side effects
- Low doses(haloperidol 0.5-1mg) given once or twice a day are usually sufficient
- The newer atypical antipsychotics(risperidone and clozaril) with effects on dopamine and serotonin have also been beneficial but may have extrapyramidal side effect profile
- A late afternoon or early evening dose may lessen the day time sedation and decrease "sundowning"
- The benefits of these psychotropic medications are variable and individualised effects are seen and also are limited by the side effects
- These drugs are useful and can improve behaviour functioning, easing the patient's distress
- Antipsychotics have severe and permanent side effects and their use must be minimised. It is indicated only for those symptoms that are harmful and distressing to the patients that cannot be controlled through other means
- Because the disease is progressive, therapy should be evaluated at least every 6 months to ensure that the fewest drugs are being used in the lowest effective doses

Representative doses of psychotropic medications in Alzheimer's disease:

Antidepressants:

DRUG	DOSE
Fluoxetin	10mg
Nortriptyline	10mg
Paroxetin	10mg
Phenelzine	15mg
Sertaline	25mg

Anxiolytics:

DRUG	DOSE
Alprazolam	0.25mg
Buspirone	5mg
Lorazepam	0.5mg
Oxazepam	10mg

Antipsychotics:

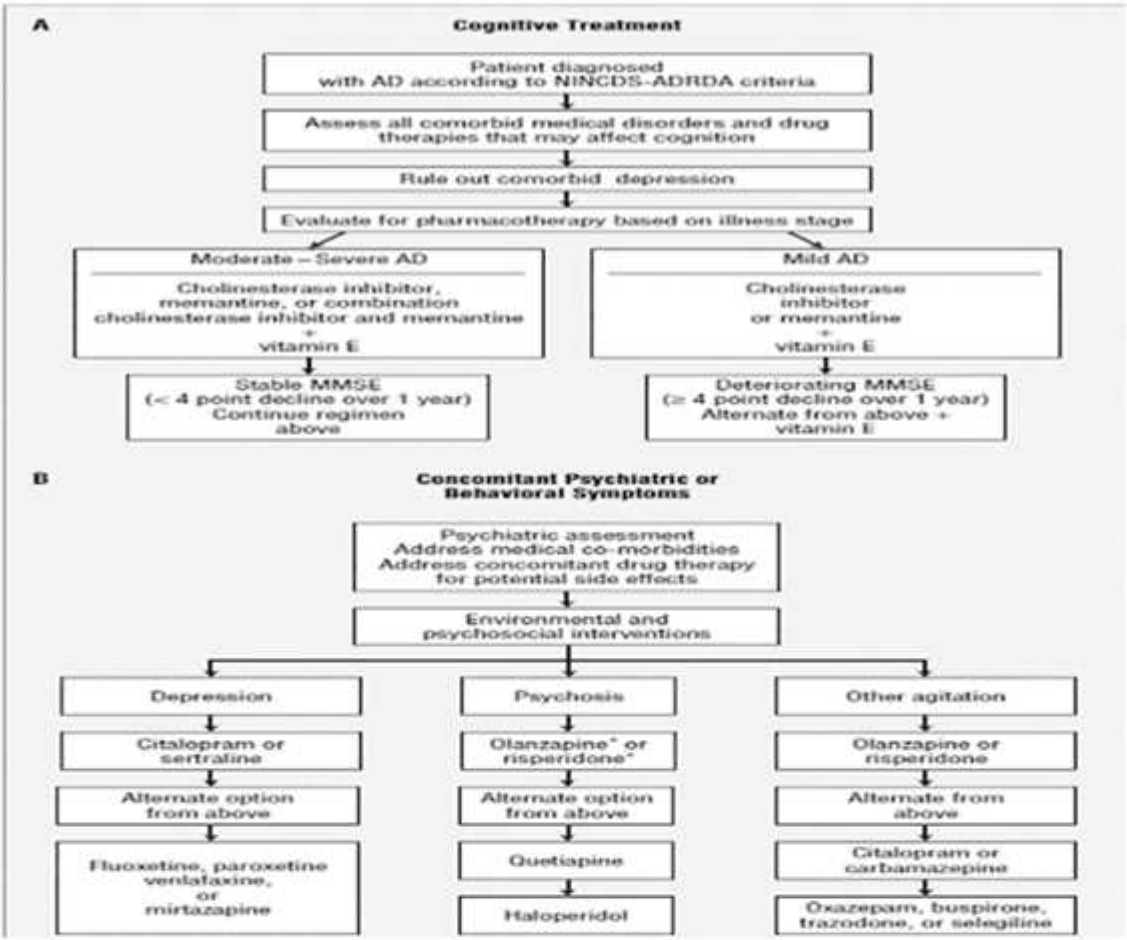
DRUG	DOSE
Clozapine	25mg
Haloperidol	0.5mg
Risperidone	1mg
Thioridazine	10mg
Thiothixene	1mg

Hypnotics:

DRUG	DOSE
Chloral hydrate	250-500mg
Temazepam	7.5mg
Triazolam	0.125mg
Zolpidem	5mg

Therapeutic treatment of Alzheimer's disease

These drugs are being developed to slow progression of brain failure or reverse or alleviate disease symptoms in Alzheimer's disease patients



1. Metabolic Enhancers

- Ergoloid mesylates FDA approved for use in the cognitive decline of the elderly
- A mixture of the methane sulfonate salts of three dihydrogenated ergot alkaloids (dihydroergocristine, dihydroergocornine, and alpha- and beta-dihydroergocryptine)
- Originally thought to act as a cerebral vasodilator, ergoloid mesylates are now classified as metabolic enhancers
- Modulate synaptic neurotransmission
- Alters glucose and oxygen utilization
- Act as α-adreno-receptor blockers and as serotonin and dopamine agonists
- Should be given early in the course of dementia
- Contraindicated in individuals who have previously shown hypersensitivity to the drug and history of psychosis

2. Cholinergic agents

- The cholinergic deficit hypothesis provides the most viable and consistent explanation for the memory impairment that occurs during Alzheimer's but it does not account for all the clinical deficits that occur

- Comparisons between Alzheimer's disease patients and age matched controls have demonstrated neuron losses in the nucleus basalis of Meynert, an area that is thought to provide cholinergic input and a major cholinergic pathway leading from the septum to hippocampus, a structure that is critical to normal memory function

Several pharmacological efforts to augment cholinergic activity have focused on:

1. Increasing the acetyl choline synthesis and release
2. Limiting the acetyl choline breakdown by inhibiting acetylcholine esterase and
3. Directly stimulating the acetylcholine receptors

Agents such as choline and lecithin serve as precursors to acetylcholine

Lecithin(phosphatidyl choline) raises the plasma choline level

Examples of Cholinergic agents

- Donepezil
- Rivastigmine
- Physostigmine
- Tacrine
- Galantamine
- Cholinesterase inhibitors block the acetylcholinesterase(AChE) and increase the availability of the Ach in the synaptic cleft by limiting its breakdown
- AChE inhibitors have been used most extensively
- Administered both intravenously and orally
- Use of physostigmine is limited because of its short duration of action and adverse effects such as nausea, vomiting, diarrhoea, dizziness and headache

Tacrine

- Has a longer duration of action than physostigmine

- Elevates Ach levels in the cerebral cortex and has shown encouraging results

- Dose related benefits in cognitive function such as performance of recognition and attentional tasks and improved measures of quality life
- Nausea, vomiting, diarrhoea and anorexia are common dose related side effects
- High prevalance of abnormal liver function tests
- Should be used with caution in patients with GIT diseases, as it may increase gastric acid secretion and cardiovascular conditions
- Has a vagotonic effect on the pulse rate and can cause bradycardia with sick sinus syndrome (sinus node dysfunction)
- Metabolised by cytochrome P450 system
- Given 4 times a day in an empty stomach
- Therapy initiated at 10mg, four times a day for 6 weeks with transaminase levels measures every other week

Donepezil

- Piperidine cholinesterase inhibitor with specificity for inhibition of acetylcholinesterase
- Fewer peripheral side effects (such as nausea, vomiting, and diarrhoea) than with nonspecific cholinesterase inhibitors
- Beneficial in patients with moderate to severe AD
- Initiated at a 5-mg/day dose in the morning and titrated to 10 mg/day after 4 to 6 weeks if it is well tolerated
- Side effects nausea, vomiting and diarrhoea

Rivastigmine

- Has central activity at acetylcholinesterase and butyrylcholinesterase, but low activity at these sites in the periphery
- Should be initiated at a dose of 1.5 mg twice daily and titrated upward at a minimum of 2-week intervals to a maximum daily dose of 12 mg
- Not metabolized through the CYP450 enzyme system
- Cholinergic side effects are the most common adverse effects

Galantamine

- Allosteric potentiating ligand of human nicotinic acetylcholine receptors
- Weak competitive and reversible cholinesterase inhibitor in all areas of the body
- Increases the concentration and thereby action of acetylcholine in certain parts of the brain
- Modulate the nicotinic cholinergic receptors on cholinergic neurons to increase acetylcholine release
- It is recommended that a patient be continued on the maximum tolerated dosage, as accelerated cognitive deterioration has been seen with dosage reductions
- Should be initiated at 8 mg/day with dosage titration of 8 mg/day occurring at 4-week intervals
- Metabolized through the CYP450 2D6 and CYP450 3A4 pathways

3. Other Agents

Memantine

- NMDA-antagonist
- First in a novel class of Alzheimer's disease medications acting on the glutamatergic system by blocking NMDA receptors
- Currently indicated for use in AD patients with moderate to severe illness
- Has 100% bioavailability regardless of administration with or without food. Protein binding is low
- Metabolism is minimal and is excreted through urine unchanged
- The half-life ranges from 60 to 100 h
- Should be initiated at 5 mg once a day and increased weekly by 5 mg a day to the effective dose of 10 mg twice daily
- Vitamin E and Selegiline
- Lipid lowering agents
- Gingo biloba
- Antiinflammatory agents- NSAIDS

GUIDELINES FOR CARE OF PATIENT WITH ALZHEIMER'S DISEASE

- Provide a calm,quiet environment
- Provide a consistent routine

- Perform adls at same time each day
- Avoid changes in routine or environment
- Reassure and explain frequently
- Do not argue with the patient
- Protect safety
- Patient at increased risk of accidents
- Eliminate caffeine from the diet

GUIDELINES FOR CARE OF THE CONFUSED PATIENT

- Provide activities to distract the patient from inappropriate behavior
- Maintain a regular routine
- Use patience and understanding
- Maintain a calm, quiet environment
- Use simple, clear words and sentences
- Give frequent praise and reassurance
- Use touch and other forms of nonverbal communication
- Use reality orientation

REALITY ORIENTATION

Helps the confused patient with reality by frequent reminders of:

- who he is
- where he is
- what time it is

Always call the patient by name and identify yourself

Repeat the date, time, and place to the patient throughout the day

GUIDELINES FOR CARE OF THE AGGRESSIVE/COMBATIVE PATIENT

- Do not respond in anger
- Leave and come back later if possible

- Be aware of warning signs of anger, such as muscle tension, restlessness, and pacing, crying, and loud speech
- Offer distractions
- Communicate and reassure
- Be aware of your nonverbal communication
- Sit down, you will appear less threatening
- Do not touch the patient without his permission

Summary

- The prevalence of Alzheimer's disease (AD) increases with each decade of life and is more common in females.
- Neuritic plaques and neurofibrillary tangles are the pathologic hallmarks of AD.
- AD affects multiple areas of cognition and is characterized by a gradual onset with a slow progressive decline.
- Early initiation and continued, uninterrupted treatment provide the optimal cognitive benefit.
- Pharmacotherapy for AD focuses on impacting three domains: cognition, psychiatric symptoms, and activities of daily living.
- Cholinesterase inhibitors and memantine are used to treat cognitive symptoms of AD.
- Slow medication dosage titration with careful monitoring should be done to minimize the incidence of troubling adverse drug reactions.

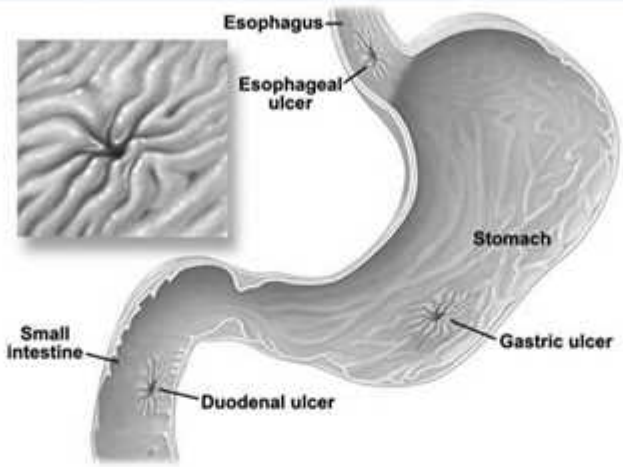
Peptic Ulcer

- Breach in the mucosa of the alimentary tract, which extends through the muscularis mucosa into the submucosa or deeper
- Chronic and most often solitary, lesions
- Any portion of gastrointestinal tract exposed to the aggressive action of acid-peptic juices
- Erosion of GI mucosa resulting from digestive action of HCl and pepsin

Duodenal vs gastric ulcers

	DUODENAL	GASTRIC
INCIDENCE	More common	Less common

ANATOMY	First part of duodenum – anterior wall	Lesser curvature of stomach
DURATION	Acute or chronic	Chronic
MALIGNANCY	Rare	Benign or malignant



Peptic ulcer

Imbalance between aggressive & protective factors

Aggressive factors

- Gastric acid
- Proteolytic enzyme

Protective factors

- Mucosal layer
- Bicarbonate secretion
- Prostaglandins

Risk factors of peptic ulcers

- *Helicobacter pylori*
- Non Steroidal Anti-inflammatory Drugs
- Steroid therapy
- Smoking and Excess alcohol intake
- Genetic factors

- Zollinger Ellison syndrome – rare syndrome caused by gastrin-secreting tumour
- Blood group O and Hyperparathyroidism

Pathophysiology of peptic ulcers

Gastric acid and pepsin

- Potential for producing mucosal damage is related to the secretion of gastric (hydrochloric) acid and pepsin
- Hydrochloric acid - parietal cells - receptors for histamine, gastrin, and acetylcholine
- Increased acid secretion - duodenal ulcers - HP infection
- Patients with ZES have gastric acid hypersecretion resulting from a gastrin-producing tumor
- Patients with gastric ulcer - normal or reduced rates of acid secretion

Mucosal defense mechanisms

- Protect the gastroduodenal mucosa from noxious endogenous and exogenous substances
- Bicarbonate barrier protect the stomach from the acidic contents
- Epithelial cell restitution, growth, and regeneration
- Maintenance of mucosal integrity and repair is mediated by the production of endogenous prostaglandins

H. pylori *infection*

Mechanisms include:

1) Direct mucosal damage
2) (b) Alterations in the host immune/inflammatory response
3) Hypergastrinemia leading to increased acid secretion

- Virulence factors (vacuolating cytotoxin, cytotoxin-associated gene protein, and growth inhibitory factor)
- Elaborating bacterial enzymes (lipases, proteases, and urease), and adherence
- Lipases and proteases degrade gastric mucus
- Ammonia produced by urease - toxic to epithelial cells

- Bacterial adherence enhances uptake of toxins into gastric epithelial cells

NSAID Induced

- Direct or topical irritation of the gastric epithelium and
- Systemic inhibition of endogenous mucosal prostaglandin synthesis
- Inhibit both COX-1 and COX-2 to varying degrees
- Neutrophil adherence may damage the vascular endothelium
- Lead to a reduction in mucosal blood flow
- Liberate oxygen-derived free radicals and proteases

Symptoms of peptic ulcers

- Abdominal pain that is often epigastric - burning - vague discomfort, abdominal fullness, or cramping
- A typical nocturnal pain that awakens the patient from sleep
- Severity of ulcer pain varies from patient to patient
- May be seasonal, occurring more frequently in the spring or fall
- Episodes of discomfort usually occur in clusters lasting up to a few weeks followed by a pain-free period or remission lasting from weeks to years
- Heartburn, belching, and bloating often accompany the pain
- Nausea, vomiting, and anorexia

Complications of peptic ulcers

- Obstruction – pyloric stenosis and duodenal stenosis
- Hemorrhage – blood in stools; if chronic – leads to anemia
- Perforation
- Malignant transformation to carcinoma

Summary

- Ulcers are defined as a breach in the mucosa of the alimentary tract, which extends through the muscularis mucosa into the submucosa or deeper

- Etiological factors are helicobacter pylori infection, nonsteroidal anti-inflammatory drugs, critical illness, hypersecretion of gastric acid , viral infections ,vascular insufficiency

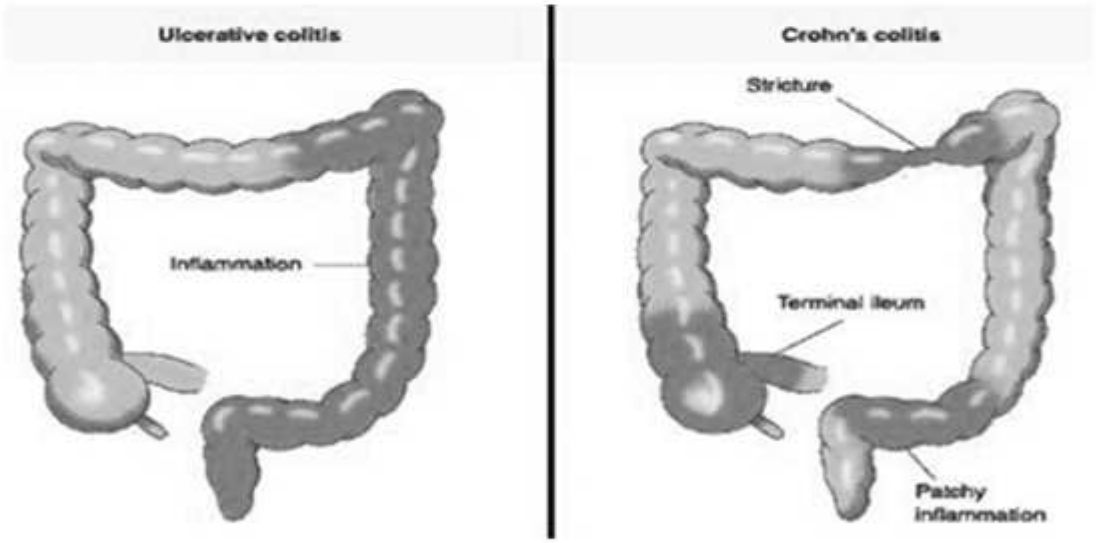
- HP infection alters host inflammatory response and damages epithelial cells directly by cell-mediated immune system whereas NSAID cause direct irritation to epithelium and decrease PGE2

Inflammatory bowel disease

Inflammatory bowel disease describes two major chronic nonspecific inflammatory disorders of the gastro intestinal tract

- They are:
- Crohn's disease(CD)
- Ulcerative colitis(UC)
- Main difference between Crohn's disease and UC is the location and nature of the inflammatory changes
- Crohn's can affect any part of the gastrointestinal tract, from mouth to anus , although a majority of the cases start in the terminal ileum
- Ulcerative colitis, in contrast, is restricted to the colon and the rectum

Ulcerative colitis and Crohn's



Etiology of Inflammatory bowel disease

- Infectious agents
  - Viruses (e.g., measles)
  - L-Forms of bacteria
  - Mycobacteria
  - Chlamydia
- Genetics
  - Metabolic defects
  - Connective tissue disorders
- Environmental Factors
  - Diet
  - Smoking (Crohn's disease)
- Immune defects
  - Altered host suceptibility
  - Immune-mediated mucosal damage
- Psychologic factors
  - Stress
  - Emotional or physical trauma
  - Occupation

Epidemology of Inflammatory bowel disease

	Ulcerative colitis	Crohn's disease
Incidence (US)	11/100 000	7/100 000
Age of onset	15-30 & 60-80	15-30 & 60-80
Male:female ratio	1:1	1,1-1,8:1
Smoking	May prevent disease	May cause disease
Oral contraceptive	No increased risk	Relative risk 1,9
Appendectomy	Not protective	Protective
Monozygotic twins	8% concordance	67% concordance

INFLAMMATORY RESPONSE

- Inflammatory response with IBD may indicate abnormal regulation of the normal immune response or an autoimmune reaction to self-antigens - microflora of the gastrointestinal tract may provide an environmental trigger to activate inflammation

- Crohn's disease has been described as "a disorder mediated by T lymphocytes which arises in genetically susceptible individuals as a result of a breakdown in the regulatory constraints on mucosal immune responses to enteric bacteria"

INFECTIOUS FACTORS

- Microorganisms are a likely factor in the initiation of inflammation in IBD - Patients with inflammatory bowel diseases have increased numbers of surface-adherent and intracellular bacteria

- Suspect infectious agents include the measles virus, protozoans, mycobacteria, and other bacteria

- Bacteria elaborate peptides (e.g., formyl-methionylleucyl-phenylalanine) that have chemotactic properties - influx of inflammatory cells with subsequent release of inflammatory mediators and tissue destruction

GENETIC FACTORS

- Genetic factors predispose patients to inflammatory bowel diseases, particularly Crohn's disease - studies of monozygotic twins, there has been a high concordance rate, with both individuals of the pair having an IBD (particularly Crohn's disease) - first-degree relatives of patients with IBD had a 13-fold increase in the risk of disease

- Other investigators - genetic markers - more frequent in those with IBD (particularly major histocompatability complex, HLA-DR2 for ulcerative colitis and HLA-A2 for Crohn's disease)

IMMUNOLOGICAL MECHANISMS

- Inflammatory process is a component of wound healing, the inflamed mucosa activates the typical inflammation –associated genes and genes associated with wound healing

- Pro-inflammatory antigenic triggers in the intestinal lumen activate macrophages and t-helper lymphocytes to release inflammatory mediators

Pathophysiology of Inflammatory bowel disease

Ulcerative colitis:

- UC is confined to be in rectum and colon and affects the mucosa and the sub mucosa - some instances, a short segment of terminal ileum may be inflamed

- Primary lesion of uc occurs in the crypts of the mucosa (crypts of liberkhun) in the form of crypt abscess

- Necrosis of the epithelium occurs and visible only in microscope

- Other typical ulceration patterns include a "collar button ulcer", which results from extensive sub mucosal undermining at the ulcer edge which results in diarrhea and bleeding

- UC complications can be local (colon/rectum) or systemic

- Complications could be minor, serious or life threatening

- Minor complication occurs in the majority of ulcerative colitis patients. They include: hemorrhoids, anal fissures or perirectal abscesses

- Major complication is toxic megacolon (1-3%), massive colonic hemorrage

- Risk of colon cancer begins to increase after 10-15 years of uc diagnosis

Ulcerative colitis – microscopic features

- Process is limited to the mucosa and submucosa with deeper layer unaffected
- Two major histologic features:

- the crypt architecture of the colon is distorted

- some patients have basal plasma cells and multiple basal lymphoid aggregates

- 40-50% of patients have disease limited to the rectum and rectosigmoid
- 30-40% of patients have disease extending beyond the sigmoid
- 20% of patients have a total colitis
- Proximal spread occurs in continuity without areas of uninvolved mucosa

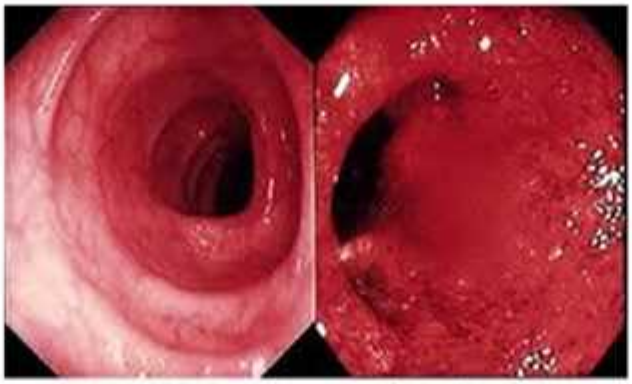
Symptoms of Ulcerative colitis

Clinical Presentation of Ulcerative Colitis

Signs and symptoms
- Abdominal cramping
- Frequent bowel movements, often with blood in the stool
- Weight loss
- Fever and tachycardia in severe disease
- Blurred vision, eye pain, and photophobia with ocular involvement
- Arthritis
- Raised, red, tender nodules that vary in size from 1 cm to several centimeters

Physical examination
- Hemorrhoids, anal fissures, or perirectal abscesses may be present
- Iritis, uveitis, episcleritis, and conjunctivitis with ocular involvement
- Dermatologic findings with erythema nodosum, pyoderma gangrenosum, or aphthous ulceration

Laboratory tests
- Decreased hematocrit/hemoglobin
- Increased erythrocyte sedimentation rate
- Leukocytosis and hypoalbuminemia with severe disease



Crohn's disease:

- Target point for CD- terminal ileum
- About two-thirds of patients have some colonic involvement, and 15% to 25% of patients have only colonic disease
- Bowel wall injury is extensive and the intestinal lumen is often narrowed
- Mesentery first becomes thickened and edematous and then fibrotic
- Ulcers tend to be deep and elongated and extend along the longitudinal axis of the bowel, atleast into the submucosa
- "Cobblestone" appearance of the bowel wall results from deep mucosal ulceration intermingled with nodular submucosal thickening
- Fistula formation is common and occurs much more frequently than with ulcerative colitis
- Fistulae often occur in the areas of worst inflammation, where loops of bowel have become matted together by fibrous adhesions
- Nutritional deficiencies are common with Crohn's disease
- Weight loss, growth failure in children, iron deficiency anemia, vitamin B12 deficiency, folate deficiency, hypoalbuminemia, hypokalemia, and osteomalacia

Sign & Symptoms of Crohn's disease

Clinical Presentation of Crohn's Disease

Signs and symptoms
- Malaise and fever
- Abdominal pain
- Frequent bowel movements
- Hemotachezia
- Fistula
- Weight loss
- Arthritis

Physical examination
- Abdominal mass and tenderness
- Perianal fissure or fistula

Laboratory tests
- Increased white blood cell count and erythrocyte sedimentation rate

Dignosis of Crohn's disease

- The first clue in the diagnosis of IBD are the symptoms:
- Unrelenting diarrhea
- Blood or mucus in the stool (more common with ulcerative colitis than Crohn's disease)
- Fever
- Abdominal pain

TESTS :

- Complete blood cell (CBC) count,
- Electrolyte panel, and
- Liver function tests (LFT)
- **Fecal occult blood test** (also called stool gaiac or hemoccult test)

OTHER TESTS

- X-RAY
- BARIUM ENEMA
- COLONOSCOPY

- ENDOSCOPY
- SIGMOIDOSCOPY

Comparision of Ulcerative colitis & Crohn's disease

Features	Ulcerative colitis	Crohn's
Abdominal pain	Variable	Common
Depth of inflammation	Mucosal	Transmural
Diarrhea	Severe	Less severe
Fistula and sinus tracts	Rare	Common
Distribution	Diffuse, contiguous spread; always involves rectum; spares proximal gastrointestinal tract	Segmental, noncontiguous spread ("skip lesions"); less common rectal involvement; occurs in entire GIT

Clinical Features of Ulcerative colitis & Crohn's disease

	UC	Crohn's disease
Blood in stool	Yes	Occasionally
Mucus	Yes	Occasionally
Systemic symptoms	Occasionally	Frequently
Pain	Occasionally	Frequently
Abdominal mass	Rarely	Yes
Perineal disease	No	Frequently

SUMMARY

- Inflammatory bowel disease describes two major chronic nonspecific inflammatory disorders of the gastro intestinal tract ulcerative colitis and crohns disease
- Major causes of inflammatory bowel disease are infectious agents, environmental factors, genetics, diet
- UC is confined to be in rectum and colon and affects the mucosa and the sub mucosa by release of inflammatory cells
- Ulcers in crohn's tend to be deep and elongated and extend along the longitudinal axis of the bowel, into the submucosa

Jaundice

Normal Range of Bilirubin

- 1～16□mol/l (0.1 ～1mg/dl)
  4/5 are unconjugated bilirubin, others are conjugated bilirubin.
- <1mg/dl normal
- 1-2mg/dl occult Hyperbilirubinemia
- >2mg/ dl jaundice Hyperbilirubinemia

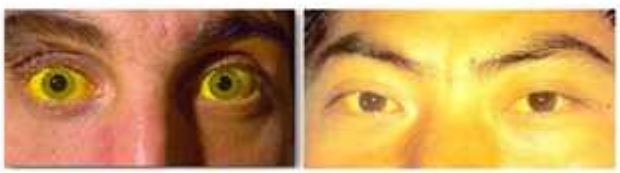
Hyperbilirubinemia

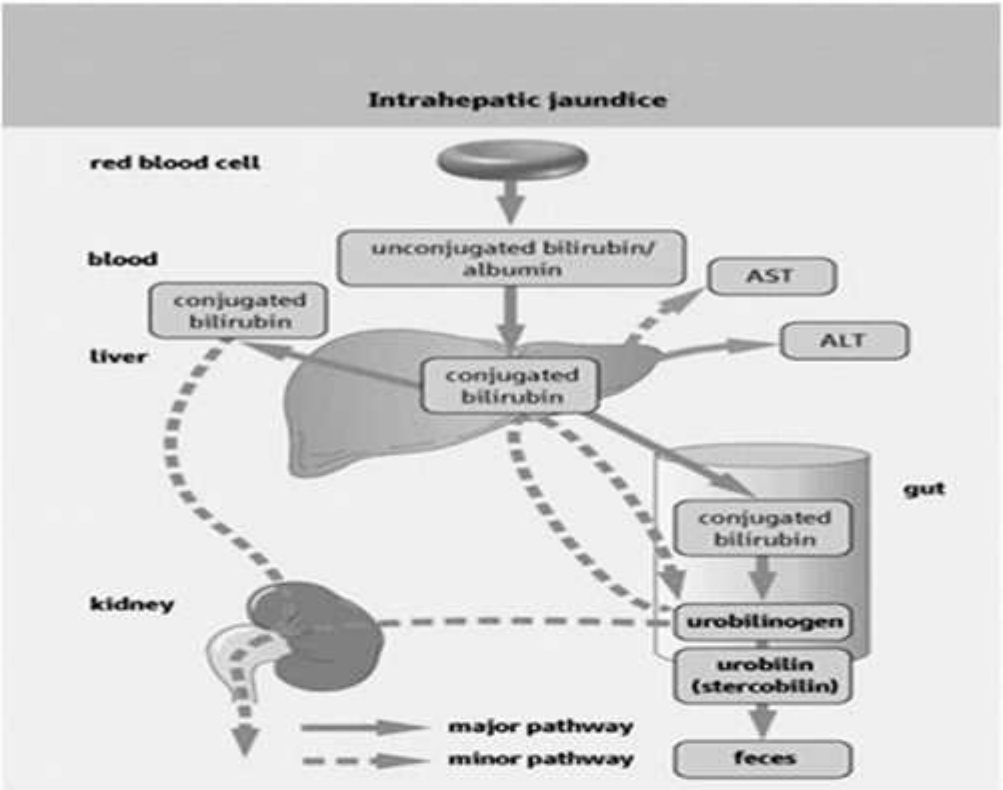
Hyperbilirubinemia: the concentration of blood bilirubin are more than 1mg/dl.

Occult: the concentration of blood bilirubin are increased, but have no clinic sympotom, normally 1-2mg/dl.

Jaundice: (also called icterus) refers to the yellow color of the skin and scleare caused by deposition of bilirubin, secondry to increased bilirubin levels in the blood.

Although not a disease itself, jaundice is usually a symptom of an underlying disorder.





Mechanism of Jaundice

Based on pathophysiology, jaundice may result from one or more of the following mechanism:

1. Increased bilirubin production (excessive red cell destruction)

2. Decreased hepatic uptake (ligandin, drug, prolonged starvation, and sepsis)

Decreased hepatic conjugation (enzyme,drugs, cirrhossis)

3. Decreeased excretion of bilirubin into bile (gallstone, tumour)

Simple Classification of Jaundice

- Accordingly, a simple classification of jaundice is to divided into 3 predominant type:

① Pre-hepatic (hemolytic jaundice)

② Hepatic jaundice

③ Post – hepatic cholestatic (obstructive jaundice)

Hemolytic Jaundice

massive lysis of red blood cells (for example, in patients with sickel cell anemia or malaria) may produce bilirubin faster than the liver can conjuagte it.

More bilirubin is excreted into the bile, the amount of the urobilinogen entering the enterohepatic circulation is increased, and urinary urobilinogen is increased.

Unconjugated bilirubin is elevated in blood.

Causes of Hemolytic Jaundice

- Malaria
- Side effects of certain drugs :antibiotic and anti-tuberculosis medicines, levodopa,
- Certain drugs in combination with a hereditary enzyme deficiency known as glucose-6-phosphate dehydrogenase (G6PD)
- Poisons Snake and spider venom, certain bacterial toxins, copper, and some organic industrial chemicals directly attack the membranes of red blood cells
- Artificial heart valves
- Hereditary RBC disorders sickle cell disease
- Enlargement of the spleen
- Diseases of the small blood vessels
- Immune reactions to RBCs cancer
- Transfusions
- Kidney failure and other serious diseases

Hepatocellular Jaundice

- Damage to liver cells (for example in patient with cirrhosis or hepatitis) causes a decrease in both bilirubin uptake and production of conjuagted bilirubin.
- Unconjugated bilirubin occur in the blood and increased urobilinogen in the urine.
- The urine is dark in color and stool are pale, clay color.
- Level of AST and ALT are elevated and the patient experience nausea and anorexia.

Obstructive Jaundice

- In this instance jaundice is results from obstruction of the bile duct.

- The presence of a hepatic tumor or bile stone may block the bile ducts, preventing passage of bilirubin into the intestine, patients with obstructive jaundice experience GI pain, nausea and produce stools that are a pale, clay color.

Sample	Indices	Normal	Obstructive Jaundice	Hemolytic Jaundice	Hepatic Jaundice
Serum	Total Bil	＜1mg/dl	＞1mg/dl	＞1mg/dl	＞1mg/dl
	Direct Bil	0～0.8mg/dl	↑↑		↑
	Indirect Bil	＜1mg/dl		↑↑	
Urine	Color	normal	deep	deeper	deep
	Bilirubin	—	＋＋	—	＋＋
	Urobilinogen	a little	↓	↑	uncertain
	Urobilin	a little	↓	↑	uncertain
Stool	Color	normal	Argilous (complete obstruction)	deeper	lighter or normal

Diagnoses of Jaundice

Differential diagnosis of jaundice

	Prehepatic	Intrahepatic	Posthepatic
conjugated bilirubin	absent	↑	↑
AST or ALT	normal	↑	normal
ALP	normal	normal	↑
urine bilirubin	absent	present	present
urine urobilinogen	present	present	absent

Summary

- The main symptom of jaundice is a yellow discoloration of the white part of the eyes (sclera) and of the skin
- Pre-hepatic jaundice is caused by anything which causes an increased rate of hemolysis
- Hepatocellular (hepatic) jaundice can be caused by acute or chronic hepatitis, hepatotoxicity, cirrhosis, drug induced hepatitis and alcoholic liver disease

- Complications of jaundice include sepsis especially cholangitis, biliary cirrhosis, pancreatitis, coagulopathy, renal and liver failure.

Hepatitis

- Inflammation of liver
- Results in damage to hepatocytes with subsequent cell death

Etiology of hepatitis

- Viral infections – Hepatitis A, B, C, D, E ; Epstein barr virus, yellow fever virus, cytomegalo virus & herpes virus
- Autoimmune chronic hepatitis
- Toxins , Alcohol
- Drugs used for the treatment of tuberculosis e.g. Isoniazid

Symptoms of hepatitis

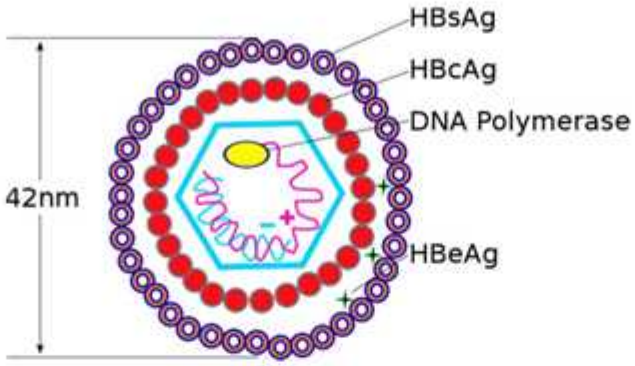
Initial symptoms	Final symptoms
Hepatic symptoms are flu like	Jaundice
Mild fever, Chills	Dark urine
Headache	Pale faeces containing puss cells
Nausea, Vomiting, Diarrhoea	Pruritis
Anorexia, Fatigue	Enlargement of spleen
Slight abdominal pain	Urticaria
Aching of joints	Dizziness, Drausiness, circulation problem

Types of hepatic viruses

Name of virus	Content	Mode of spread
Hepatitis A virus (HAV)	RNA	Faeces
Hepatitis B virus (HBV)	DNA	Parenteral, Sexual contact, Blood transfusion, Babies born to HBV infected mothers
Hepatitis C virus (HCV)	RNA	Parenteral transmission, IV drug abuse, needle sharing
Hepatitis D virus (HDV)	RNA	Super infection

Hepatitis E virus (HEV)	RNA	Transmitted enterically
Hepatits G virus (HGV)	RNA	Parenterally transmitted hepatotropic virus

Structure of HBV



- Only DNA containing virus
- Belongs to group 'hepadnaviridae'
- Diameter- 42 nm; incubation period is 6-8 weeks
- Comprises of core and a capsule
- Core consists of DNA & DNA polymerase
- Core is surrounded by markers
  - Hepatitis B core antigen (HB_c Ag)
  - Hepatitis B envelope antigen (HB_e Ag)
  - Hepatitis B surface antigen (HB_s Ag)

Mode of transmission of Hepatitis

- Present in all body secretion
- A close contact with an infected person spreads the disease
- By blood transfusion
- Not through fecal matter

Stages of hepatitis (Assessed by different markers)

Stage 1

- HB_s Ag is identified in asymptomatic phase
- It appears even before the onset of a disease
- Reaches the peak level during disease stage
- The counts become less with in 3-6 months

Stage 2

- HB_e Ag, HBV DNA, DNA polymerase appears
- HB_e Ag – indicates the progression of infection
- Continues viral replication

Stage 3

- IgM and anti HB_c is detected
- Ab is identified just before the onset of symptoms
- After several months of infections IgG and anti HB_c

Phases of HBV infection

Proliferative phase

- Shows the presence of symptoms
- DNA of HBV has accessory replicative chromosomes and forms virions
- HB_s antigen binds with MHC class molecule and activated CD8+ T-cells

Integrative phase

- Viral DNA gets incorporated into the host genome
- Damage of hepatocytes by activation of CD8+ T- cells

Types of Hepatitis

Acute hepatitis – comprises of 4 phases

1. Incubation period –depends on type of virus

- HAV – 12 weeks
- HBV – 10 weeks

- HCV – 7 weeks
- HDV – 6 weeks
- HEV – 2-8 weeks

Patient does not show any signs or symptoms in incubation period

2. Symptomatic pre – icteric phase

- Non specific symptoms like fatigue, nausea, vomiting, weight loss, low fever, headache, muscle & joint aches, diarrhoea

3. Symptomatic icteric phase

- Yellow coloration appears
- Jaundice appears in 3rd stage

4. Phase of recovery

- Takes place depending upon the severity of infection

Chronic hepatitis

- Hepatic diseases remain for more than 6 months
- Inflammation & necrosis takes place
- Fatigue, Malaise, Lack of apetite, mild jaundice
- Symptoms are highly variable & not predictive in nature

Summary

- Hepatitis is inflammation of liver that results in damage to hepatocytes with subsequent cell death
- It may occur due to viral , autoimmune chronic hepatitis, Toxins, Alcohol and drugs
- HBV is main causative organism
- Types of hepatitis include acute and chronic

Alcoholic Liver Disease

Alcoholic liver disease is the term used to describe the spectrum of liver injury associated with acute and chronic alcoholism

Signs and Symptoms

- Progresses in the liver as inflammation (hepatitis) and leads to fatty liver and cirrhosis

Risk factors

- Occurs after many years of excessive drinking

- Acute alcoholic hepatitis – Binge drinking
- Severe drinking – Life threatening
- Genetic factors - Women have increased susceptibility to develop advanced alcoholic liver disease with much lesser alcohol intake
- Malnutrition
- Toxicity of ethanol in liver
- Infection – Hepatitis C infection

Distinctive forms of Alcoholic Liver Disease

Hepatic Steatosis (Fatty liver)

- Moderate consumption - Deposition of small lipid droplets in hepatocytes
- Excessive consumption – accumulation of lipids in macrovascular droplets
- Nucleus gets displaced, Enlarged liver

Alcoholic hepatitis

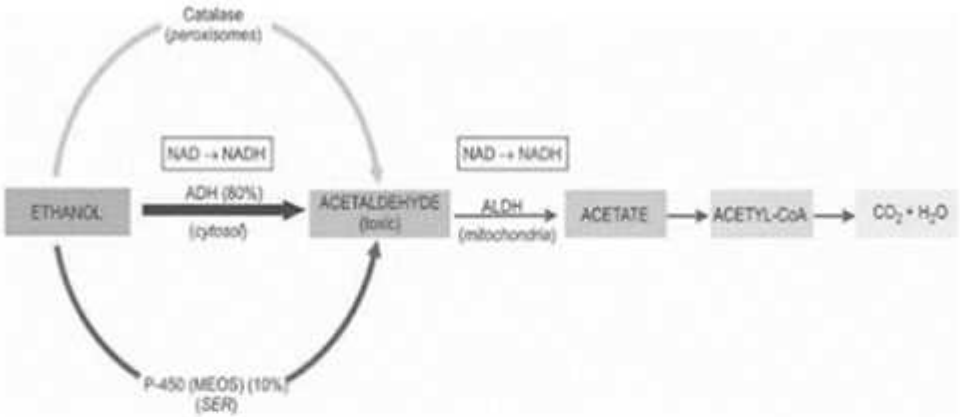
- Necrosis of liver cells in centrilobular region
- Neutrophillic reaction
- Fibrosis

Alcoholic Cirrhosis

- Irreversible - Final stage
- Liver turns brown, shrunken and non-fatty appearance
- Resembles post necrotic cirrhosis

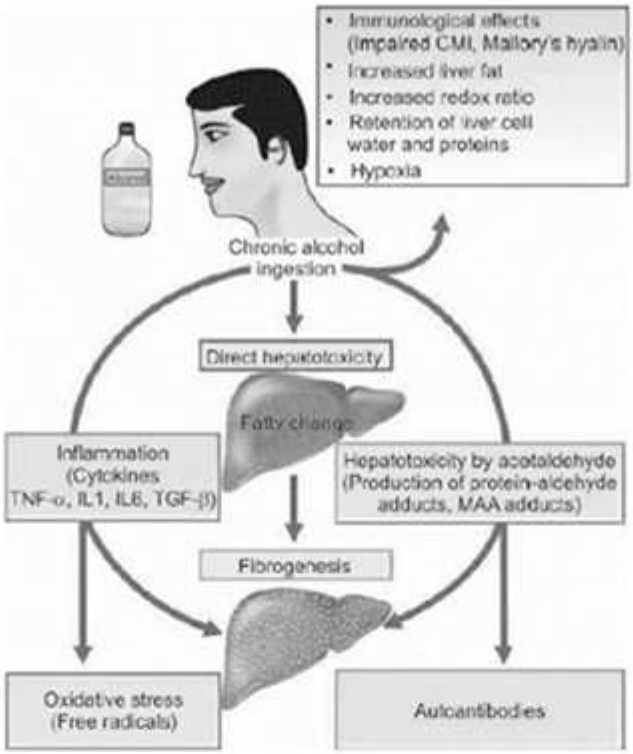
Pathogenesis of Alcoholic Liver Disease

Ethanol Metabolism



ADH = Alcohol Dehydrogenase; **ALDH or ACDH** = Hepatic Acetaldehyde Dehydrogenase; **NAD** = Nicotinamide Adenine Dinucleotide; **NADH** = Reduced NAD

- Direct hepatotoxicity by ethanol to microtubules, mitochondria, membrane hepatocytes
- Hepatotoxicity by ethanol metabolites
  - Production of protein-aldehyde adducts
  - Formation of malo-di-aldehyde-acetaldehyde (MAA)
- Oxidative Stress - oxidation of ethanol by cytochrome 450 oxidase, generation of free radicals and oxidative damage
- Immunological attacks on hepatocytes
- Fibrogenesis
  - Damaged hepatocytes,
  - Malon-di-aldehyde-acetaldehyde adducts,
  - Activated kupffer cells, and
  - Direct stimulation by acetaldehyde



Laboratory Diagnosis For Alcoholic Liver Disease

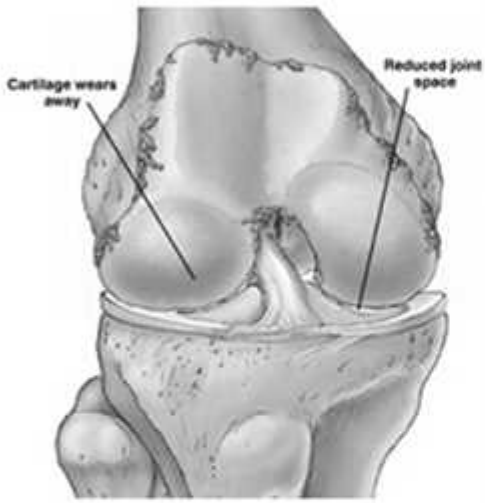
- Elevated transaminases: increase in SGOT (AST) is more than that of SGPT (ALT)
- Rise in serum γ-glutamyl transpeptidase (γ-GT)
- Elevation in Serum alkaline phosphatase
- Hyperbilirubinaemia
- Hypoproteinaemia with reversal of albumin-globulin ratio
- Prolonged prothrombin time and partial thromboplastin time
- Anemia and Neutrophilic leucocytosis

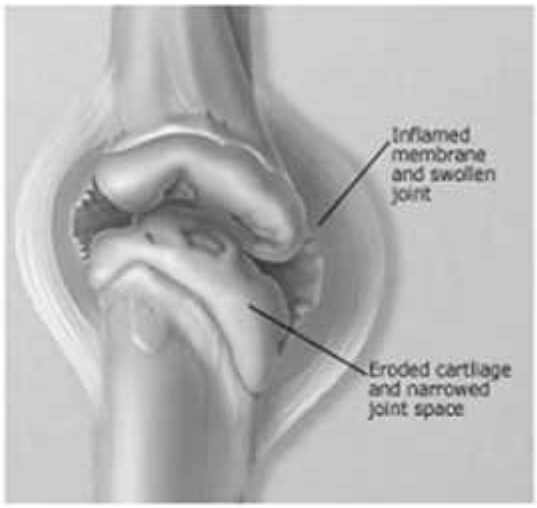
Summary

- Alcohol liver disease is damage to liver and its function due to alcohol abuse
- Progresses in the liver as inflammation (hepatitis) and leads to fatty liver and cirrhosis
- Major forms include hepatic steatosis, hepatitis, cirrhosis
- Alcohol is a caloric food source which displaces nutrients
- Causes the activation of Kupffer cells and release of proinflammatory mediators

Rheumatoid arthritis (RA

- Rheumatoid arthritis (RA) is the most common systemic inflammatory disease characterized by symmetrical joint involvement
- Extraarticular involvement, including rheumatoid nodules, vasculitis, eye inflammation, neurologic dysfunction, cardiopulmonary disease, lymphadenopathy, and splenomegaly, can be manifestations of the disease
- Although the usual disease course is chronic, some patients will enter a remission spontaneously





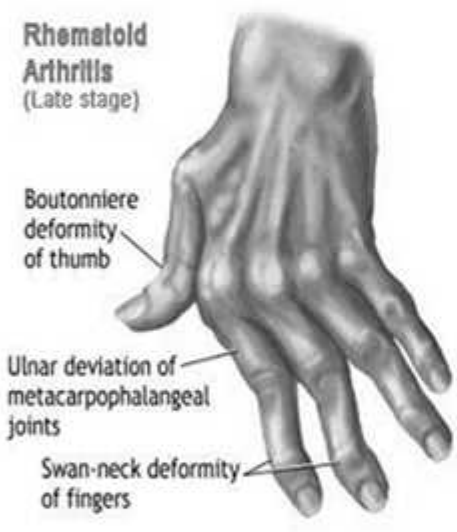
EPIDEMIOLOGY OF RHEUMATOID ARTHRITIS

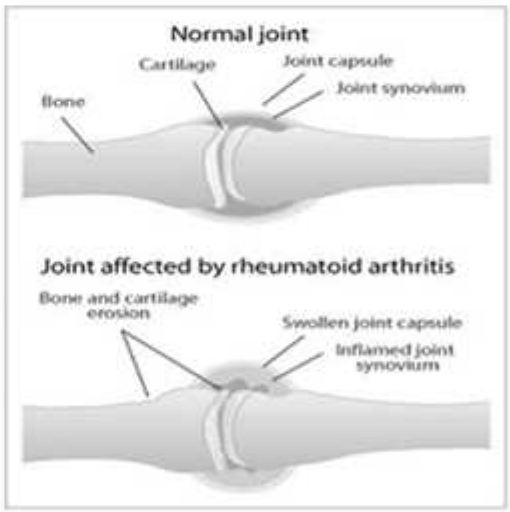
- Rheumatoid arthritis is estimated to have a prevalence of 1% and does not have any racial predilections
- It can occur at any age, with increasing prevalence up to the seventh decade of life
- The disease is 3 times more common in women
- In people ages 15 to 45 years, women predominate by a ratio of 6:1; the sex ratio is approximately equal among patients in the first decade of life and in those older than age 60 years
- Epidemiologic data suggest that a genetic predisposition and exposure to unknown environmental factors may be necessary for expression of the disease
- The major histocompatibility complex molecules, located on T lymphocytes, appear to have an important role in most patients with RA
- These molecules can be characterized using human lymphocyte antigen (HLA) typing

- A majority of patients with RA have HLA-DR4, HLA-DR1, or both antigens in the major histocompatibility complex region
- Patients with HLA-DR4 antigen are 3.5 times more likely to develop RA than those patients who have other HLA-DR antigens
- Although the major histocompatibility complex region is important, it is not the sole determinant, because patients can have the disease without these HLA types

PATHOPHYSIOLOGY OF RHEUMATOID ARTHRITIS

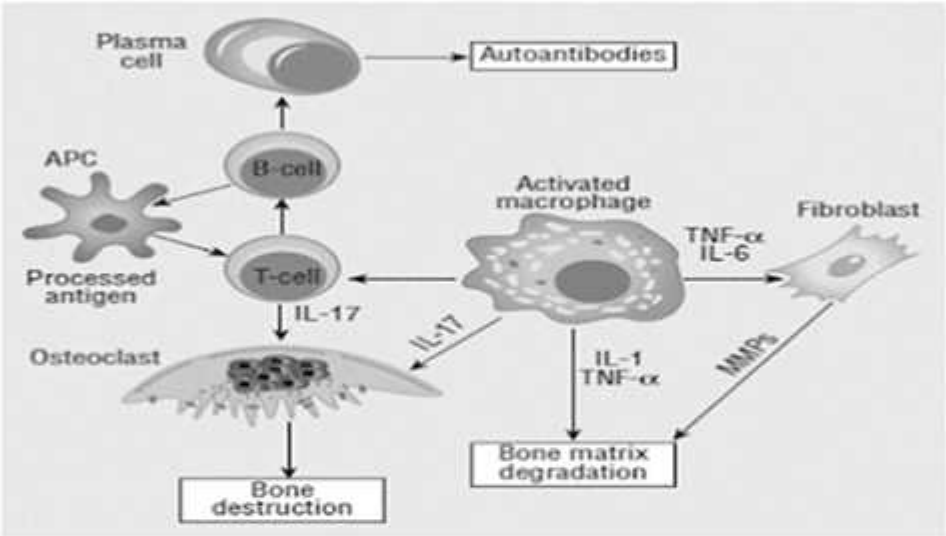
- Chronic inflammation of the synovial tissue lining the joint results in the proliferation of this tissue
- The inflamed, proliferating synovium is characteristic of rheumatoid arthritis is called *pannus*
- This pannus invades the cartilage and eventually the bone surface, producing erosions of bone and cartilage and leading to destruction of the joint





- Rheumatoid arthritis is considered to be an immune response to an unknown antigen and the antibody formed against rheumatoid arthritis is (rheumatoid factor), which is Immunoglobulin M (IgM).
- In rheumatoid arthritis immune system can no longer differentiate self from nonself tissues and attacks the synovial tissue and other connective tissues
- The immune system has both
    - humoral (B -Lymphocytes) and
    - cell-mediated (T-lymphocytes) functions.

- The humoral component is necessary for the formation of antibodies.
- Most patients with rheumatoid arthritis form antibodies called *rheumatoid factors.*
- Immunoglobulins (IgM) can activate the complement system
- The complement system encourages chemotaxis, phagocytosis, and the release of lymphokines by mononuclear cells, which are then presented to T lymphocytes.
- The processed antigen is recognized by MHC proteins on the lymphocyte, which activates it to stimulate the production of T and B cells.



- The proinflammatory cytokines tumor necrosis factor (TNF), interleukin-1 (IL-1), and interleukin-6 (IL-6) are key substances in the initiation and continuance of rheumatoid inflammation
- Activated T cells produce cytotoxins, which are directly toxic to tissues, and cytokines, which stimulate further activation of inflammatory processes and attract cells to areas of inflammation
- **Rheumatoid arthritis progresses in 3 stages:-**

  1 st Stage - Swelling of the synovial lining, causing, pain, warmth,stiffness, redness ,swelling around the joint

  2 nd Stage - Rapid division and growth of cells, or pannus, which causes the synovium to thicken

  3 rd Stage - The inflamed cells release enzymes that might damage, bone & cartilage, often causing the involved joint to loose its shape and alignment, causing more pain and loss of movement

- **Vasoactive substances** also play a role in the inflammatory process.

- Histamine, kinins, and prostaglandins are released at the site of inflammation.
- These substances increase both blood flow to the site of inflammation and the permeability of blood vessels.
- These substances cause the edema, warmth, erythema and pain
- Loss of cartilage may result in a loss of the joint space
- The formation of chronic granulation or scar tissue can lead to loss of joint motion or bony fusion (called *ankylosis)*
- This results in a loss of support to the affected joint leading to chronic deformity
- CD8 + killer T cells have a regulatory effect on the immune process by suppressing activity of CD4 + cells through release of antiinflammatory cytokines and promoting apoptosis (cell death)
- Activated T cells produce cytotoxins, which are directly toxic to tissues, and cytokines, which stimulate further activation of inflammatory processes and attract cells to areas of inflammation
- Macrophages are stimulated to release prostaglandins and cytotoxins
- T-cell activation requires both stimulation by proinflammatory cytokines as well as interaction between cell surface receptors, called co-stimulation
- One of these costimulation interactions is between CD28 and CD80/86
- The binding of the CD80/86 receptor by abatacept has proved to be an effective treatment for RA but preventing costimulation interactions between T cells
- Although it has been suggested that T cells play a key role in the pathogenesis of RA, B cells clearly have an equally important role
- Evidence for this importance may be found in the effectiveness of B-cell depletion using rituximab in controlling rheumatoid inflammation
- Activated B cells produce plasma cells, which form antibodies
- These antibodies in combination with complement result in the accumulation of polymorphonuclear leukocytes, which release cytotoxins, oxygen free radicals, and hydroxyl radicals that promote cellular damage to synovium and bone
- The benefits of B-cell depletion occur even though antibody formation is not suppressed with rituximab therapy suggesting other mechanisms play a role in reducing RA activity
- B cells produce cytokines that may alter the function of other immune cells

- They also have the ability to process antigens and act as antigen presenting cells, which interact with T cells to activate the immune process
- In the synovial membrane, CD4 + T cells are abundant and communicate with macrophages, osteoclasts, fibroblasts and chondrocytes either through direct cell–cell interactions using cell surface receptors or through proinflammatory cytokines such as TNF-*α,* IL-1, and IL-6
- These cells produce metalloproteinases and other cytotoxic substances, which lead to the erosion of bone and cartilage
- They also release substances promoting growth of blood vessels and adhesion molecules, which assists in proinflammatory cell trafficking and attachment of fibroblasts to cartilage and eventual synovial invasion and destruction
- Vasoactive substances also play a role in the inflammatory process
- Histamine, kinins, and prostaglandins are released at the site of inflammation
- These substances increase both blood flow to the site of inflammation and the permeability of blood vessels
- These substances cause -granulocytes to pass from blood vessels to the site of inflammation
- The end results of the chronic inflammatory changes are variable. Loss of cartilage may result in a loss of the joint space
- The formation of chronic granulation or scar tissue can lead to loss of joint motion or bony fusion (called *ankylosis)*
- *Laxity of tendon* structures can result in a loss of support to the affected joint, leading to instability or subluxation

Clinical Presentation

SYMPTOMS OF RHEUMATOID ARTHRITIS

- Joint pain and stiffness of more than 6 weeks' duration
- May also experience fatigue, weakness, low-grade fever, and loss of appetite
- Muscle pain and afternoon fatigue may also be present
- Joint deformity is generally seen late in the disease

SIGNS OF RHEUMATOID ARTHRITIS

- Tenderness with warmth and swelling over affected joints usually involving hands and feet

- Distribution of joint involvement is frequently symmetrical
- Rheumatoid nodules may also be present

LABORATORY TESTS FOR RHEUMATOID ARTHRITIS

- Rheumatoid factor detectable in 60% to 70%.
- Elevated erythrocyte sedimentation rate (ESR)and
- C-reactive protein are markers for inflammation.
- Normocytic normochromic anemia is common, as is thrombocytosis.

OTHER DIAGNOSTIC TESTS FOR RHEUMATOID ARTHRITIS

- Joint fluid aspiration may show increased white blood cell counts without infection, and crystals.
- Joint radiographs may show periarticular osteoporosis, joint space narrowing, or erosions.

 The symptoms of rheumatoid arthritis usually develop over the course of several weeks to months

 symptoms include fatigue, weakness, low-grade fever, loss of appetite, and joint pain

 Stiffness and muscle aches (myalgias) may precede the development of joint swelling (synovitis)

 Fatigue may be more of a problem in the afternoon

 During disease flares, the onset of fatigue begins earlier in the day and subsides as disease activity lessens

Joint Involvement

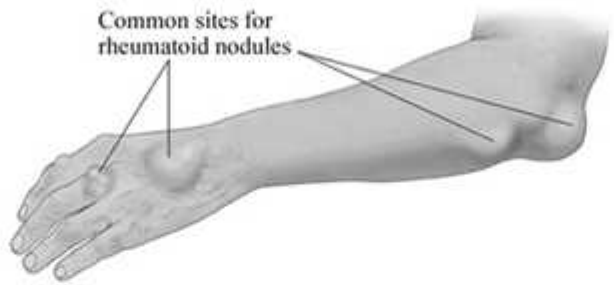
- Joint involvement tends to be symmetrical; however, early in the disease some patients present with an asymmetrical pattern involving one or a few joints that eventually develops into the more classic presentation
- About 20% of patients develop an abrupt onset of their illness with fevers, polyarthritis, and constitutional symptoms (e.g., depression, anxiety, fatigue, anorexia, and weight loss
- *No* single test or physical finding can be used to make the diagnosis of rheumatoid arthritis
- The joints affected most frequently by rheumatoid arthritis are the small joints of the hands, wrists, and feet
- In addition, elbows, shoulders, hips, knees, and ankles may be involved
- Patients usually experience joint stiffness that typically is worse in the morning

- Chronic inflammation with lack of adequate exercise program results in loss of range of motion, atrophy of muscles, weakness, and deformity
- On examination, the swelling of the joints may be visible or may be apparent only by palpation
- The swelling feels soft and spongy because it is caused by proliferation of soft tissues or fluid accumulation within the joint capsule
- The swollen joint may appear erythematous and feel warmer than nearby skin surfaces, especially early in the course of the disease
- Deformity of the hand may be seen with chronic inflammation
- These changes may alter the mechanics of hand function, reducing grip strength and making it difficult to perform usual daily activities
- Swelling at the elbow is most evident at the radiohumeral joint
- Shoulder pain may result from involvement of the joint itself or from tendon inflammation (tendinitis) or inflammation of the bursa (bursitis) near the deltoid muscle
- The knee also can be involved, with loss of cartilage, instability, and joint pain
- Foot and ankle involvement in rheumatoid arthritis is common
- The metatarsophalangeal joints are involved commonly in rheumatoid arthritis, making walking difficult
- Subluxation of the metatarsal heads leads to “cock-up” or hammer-toe deformities
- Involvement of the spine usually occurs in the cervical vertebrae; lumbar vertebral involvement is rare
- The temporomandibular joint (jaw) can be affected, resulting in difficulty in chewing food
- Inflammation of cartilage in the chest can lead to chest wall pain
- Hip pain may occur as a result of destructive changes in the hip joint, soft-tissue inflammation (e.g., bursitis), or referred pain from nerve entrapment at the lumbar vertebrae

EXTRA-ARTICULAR INVOLVEMENT

- **RHEUMATOID NODULES** (on extensor surfaces of elbows, forearms, and hands)
- **VASCULITIS** (Invasion of blood vessel walls by inflammatory cells)
- **PULMONARY COMPLICATIONS** (pleural effusion,fibrosis)

- **OCULAR MANIFESTATIONS** (keratoconjunctivitis, *Sjogren's syndrome*)
- **CARDIAC INVOLVEMENT** (pericarditis)
- **FELTY'S SYNDROME** (splenomegaly and neutropenia)
- **OTHER COMPLICATIONS** (Lymphadenopathy)



TREATMENT GOALS

- The ultimate goal is to achieve complete disease remission, although this goal is hardly ever achieved.
- Additional goals include
  - controlling disease activity and joint pain,
  - maintaining the ability to function in daily activities or work,
  - improving the quality of life,
  - slowing destructive joint changes.

Treatment of Rheumatoid arthritis

- Includes pharmacologic and nonpharmacologic therapies.

NONPHARMACOLOGIC THERAPY

- Rest (relieves stress on inflamed joints), occupational therapy (skills and exercises), physical therapy, use of assistive devices, weight reduction, and surgery are the most useful types of nonpharmacologic therapy.

Pharmacologic Therapy

- A disease-modifying antirheumatic drug (DMARD) should be started within the first 3 months of onset of symptoms of rheumatoid arthritis provides more favorable outcome.
- NSAIDs and/or corticosteroids may be used for symptomatic relief if needed.

- They provide relatively rapid improvement in symptoms compared with DMARDs
- DMARDs may take weeks to months for any benefit.
- NSAIDs have no impact on disease progression, and corticosteroid use carries a long-term risk of complications
- Commonly used DMARDs include methotrexate, hydroxychloroquine, sulfasalazine, and leflunomide
- The biologic agents that have also been demonstrated to have disease-modifying activity include
    - The anti-TNF drugs
    - The interleukin-1–receptor antagonist, anakinra
- Less frequently used are azathioprine, d-penicillamine, gold (including auranofin), minocycline, cyclosporine, and cyclophosphamide
- This is due to either less efficacy, high toxicity, or both

Osteoporosis

Definition

- **Clinical**
    - Loss of bone mass sufficient to significantly increase the risk of fracture
- **Diagnostic**
    - T score – number of standard deviations above or below the mean for a similar healthy 30 year old
        - Normal BMD = T: 0 to -1
        - Osteopenia BMD = T: -1 to -2.5
        - Osteoporosis BMD = T: less than -2.5
    - Z score – number of standard deviations above or below the mean for the patients age, sex and ethnicity

Epidemiology of Osteoporosis

- **United States**
    - 10 million individuals with osteoporosis

- 34 million individuals with osteopenia

- **Fracture Risks over age 50**
  - 50% of women will have an osteoporosis related fracture
  - 25 % of men will have an osteoporosis related fracture
- **Estimated costs**
  - Direct health care $14 billion each year

Pathogenesis of Osteoporosis

- Peak bone mass
- Etiology Bone loss
- Age
- Secondary causes

Peak Bone Mass

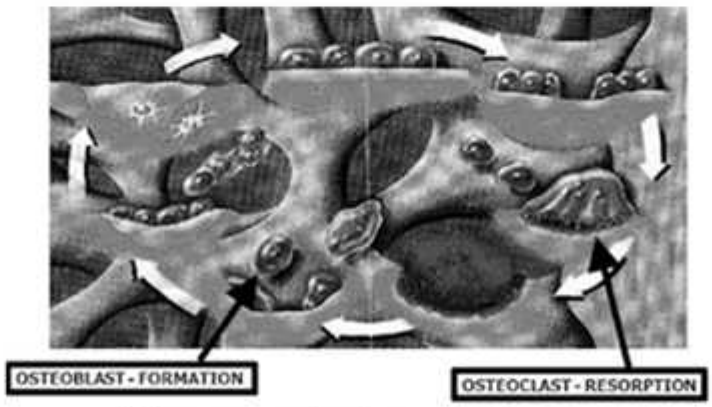
- Genetically determined
  - 70-75%
  - Driven by sex hormones during puberty
  - Depends on site measured – spine, femur, radius
- Ethnicity
  - Chinese American later than Caucasians
- Women
  - Peak accrual ages 11-15
  - 95 per cent achieved by late teens
- Men
  - Peak accrual later teens
  - Maximum spine age 20

- Radius and femur by mid twenties

Factors Affecting Peak Bone Mass

- Delay or Failure of puberty
  - *Primary Hypogonadism*
    - Turners syndrome
    - Klinefelter syndrome
    - Absent cervix, uterus, cervix and/or vagina
    - Cryptorchidism
    - Chemotherapy, Radiotherapy
    - Chronic systemic diseases
  - *Secondary Hypogonadism*
    - Kallmann syndrome
    - CNS tumors, infiltrative disorders
    - Malnutrition
    - Chronic systemic illness

Etiology of Bone loss in Osteoporosis



Primary cause is estrogen deficiency

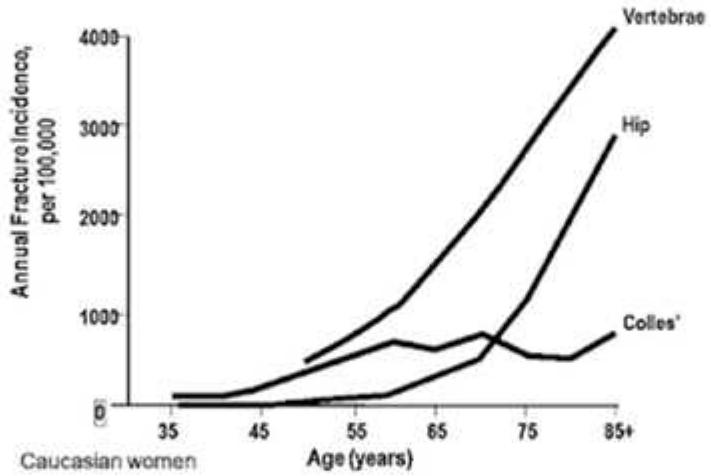
Estrogen Deficiency

- Women

- Occurs earlier
- At menopause bone loss rates to increase by 2 to 6 fold
- For subsequent 6-8 years
- Impairs calcium absorption from gut

- Men
  - Testosterone declines age
  - Estrogen declines age
  - Both androgens and estrogen contribute

Fracture Risk with Aging



Secondary Causes of Accelerated Bone-loss/Osteoporosis

- **Inherited disorders**
  - Osteogenesis imperfecta tarda
  - Thallasemia
- **Amenorrhea**
  - Eating disorders
  - Low weight
  - Excess Exercise
  - Female athlete triad

        - Energy deficiency
        - Low bone mineral density
        - Amenorrhea
    - Premature ovarian failure
- **Respiratory**
    - Cystic fibrosis
- **Gastrointestinal**
    - Celiac sprue
    - Post Gastric by pass
    - Inflammatory bowel disease
- **Renal**
    - Idiopathic hypercalciuria
    - Chronic renal failure
- **Post organ transplant**
    - Immunosuppressive therapy
- **Endocrine**
    - Hyperthyroidism
    - Hyperparathyroidism
    - Cushing's syndrome
    - Hypogonadism
    - Vitamin D deficiency
- **Rheumatology**
    - Rheumatoid arthritis
    - Seronegative athropathies

- **Lifestyle**
  - Smoking
  - Alcohol
- **Drugs**
  - *Glucocorticoids*
  - *Cyclosporine*
  - *Anti seizure medications*
    - Phenobarbital
    - Phenytoin
  - *Heparin*
  - *Chemotherapy*
    - Aromatase inhibitors
  - *Thyroxine*
    - Over replacement

Diagnosis of Osteoporosis

- Approach to patient
- Investigations
  - *Bloods*
  - *Urine*
  - *Imaging*
  - FRAX use
- Calcium and Vitamin D

Osteoporosis Investigations

- **Bloods -Basic**

- CBC
- Electrolytes and eGFR
- Serum calcium and phosphate
- TSH
- Testosterone (Men)
- Serum protein electrophoresis
- Bone markers (consider)

- **Urine**
  - 24 hour urine
  - Volume
  - Creatinine and calcium

Bone Mineral Density Testing

- Bone mineral density testing
  - Important means of assessing fracture risk
  - Not stand alone test
- Other risk factors have impact on fracture risk
  - occasionally more significant impact than bone density results alone
  - Glucorticoids
- All known risk factors should be considered when deciding to treat patients
  - Mostly treating patients based on risk
  - No overt disease
- We need better tools for assessing fracture risk

Summary

- Osteoporosis is an important public health problem

- Accurate diagnosis and treatment requires the use of bone densitometry.
- Radiologists play a central role in the diagnosis and management
  - of this disease:
  - measuring bone density
  - diagnosing fractures
  - pointing out secondary causes of bone loss

GOUT

- The term *gout describes a heterogeneous clinical spectrum of* diseases including hyperuricemia, recurrent attacks of acute arthritis associated with monosodium urate crystals in synovial fluid leukocytes, deposits of monosodium urate crystals (tophi) in tissues in and around joints, interstitial renal disease, and uric acid nephrolithiasis.
- The underlying metabolic disorder of gout is hyperuricemia, defined physiochemically as serum that is supersaturated with monosodium urate.

Epidemiology

- There is a direct correlation between serum uric acid concentration and both the incidence and prevalence of gout.
- Population studies have shown that serum urate concentration correlates with increasing age, serum creatinine, blood urea nitrogen, male gender, blood pressure, body weight, and alcohol intake.
- The incidence of gout -higher for individuals -higher amounts of meat or fish.
- Gout affects men about seven to nine times more often than women.
- The incidence of gout increases with age, peaking at 30 to 50 years of age, with an annual incidence ranging from 1 in 1,000 for men ages 40 to 44 years and 1.8 in 1,000 for those ages 55 to 64 years.
- The lowest rates of gout are observed in young women, approximately 0.8 cases per 10,000 patient-years.
- Serum uric acid levels in women approach those of men once menopause has occurred
- Gout in men younger than 30 years of age or in premenopausal women may indicate an inherited enzyme defect or the presence of renal disease

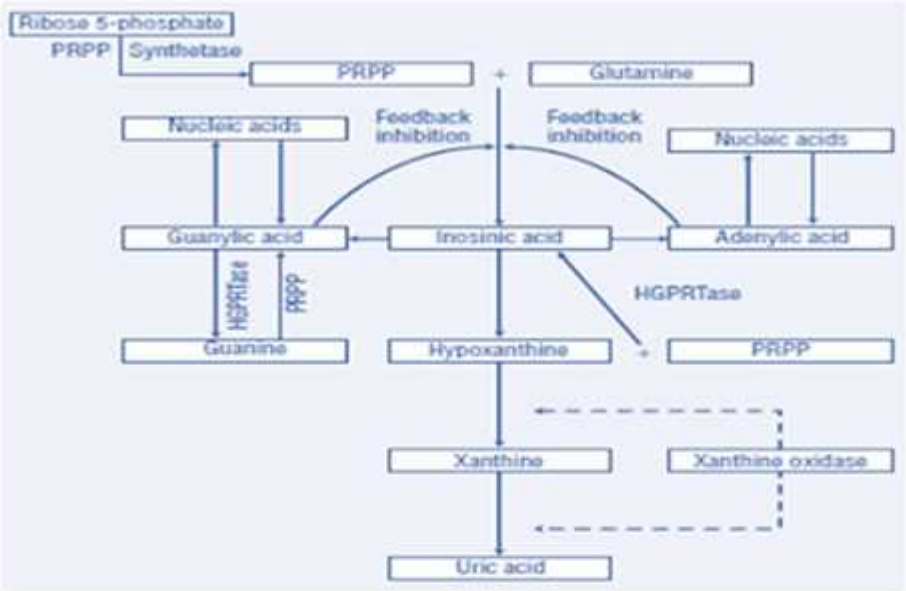
Etiology and Pathophysiology of Gout

- In humans, the production of uric acid is the terminal step in the degradation of purines.
- Normal uric acid levels are near the limits of urate solubility, because of the delicate balance that exists between the amount of urate produced and excreted.
- Humans have higher uric acid levels than other mammals because they do not express the enzyme uricase, which converts uric acid to the more soluble allantoin.
- Gout occurs exclusively in humans in whom a miscible pool of uric acid exists
- Under normal conditions, the amount of accumulated uric acid is about 1,200 mg in men and about 600 mg in women
- The size of the urate pool is increased several fold in individuals with gout.
- This excess accumulation may result from either overproduction or underexcretion of uric acid
- Several conditions are associated with either decreased renal clearance or an overproduction of uric acid, leading to hyperuricemia

OVERPRODUCTION OF URIC ACID

- The purines from which uric acid is produced originate from three sources:
  - Dietary purine
  - Conversion of tissue nucleic acid to purine nucleotides
  - De novo synthesis of purine bases
- The purines derived from these three sources enter a common metabolic pathway leading to the production of either nucleic acid or uric acid
- Under normal circumstances, uric acid may accumulate excessively if production exceeds excretion

Purine metabolism



- The average human produces about 600 to 800 mg of uric acid each day.
- Dietary purines play an unimportant role in the generation of hyperuricemia in the absence of some derangement in purine metabolism or elimination.
- Diet modifications are important for patients with such problems who develop symptomatic hyperuricemia.
- Several enzyme systems regulate purine metabolism.

Conditions Associated with Hyperuricemia

Primary gout	Obesity
Diabetic ketoacidosis	Sarcoidosis
Myeloproliferative disorders	Congestive heart failure
Lactic acidosis	Renal dysfunction
Lymphoproliferative disorders	Down syndrome
Starvation	Lead toxicity
Chronic hemolytic anemia	Hyperparathyroidism
Toxemia of pregnancy	Acute alcoholism
Pernicious anemia	Hypoparathyroidism
Glycogen storage disease type 1	Acromegaly
Psoriasis	Hypothyroidism
Hypoxanthine-guanine phosphoribosyl-transferase deficiency	Phosphoribosylpyrophosphate synthetase overactivity
Polycythemia vera	Berylliosis
Renal transplantation	

- Abnormalities in these regulatory systems can result in overproduction of uric acid.
- Uric acid may also be overproduced as

- A consequence of increased breakdown of tissue nucleic acids
- Excessive rates of cell turnover
- Myeloproliferative and lymphoproliferative disorders
- Polycythemia vera
- Psoriasis
- Some types of anemias

- Cytotoxic medications used to treat these disorders can result in overproduction of uric acid secondary to lysis and breakdown of cellular matter.
- Two enzyme abnormalities resulting in an overproduction of uric acid have been well described
- The first is an increase in the activity of phosphoribosyl pyrophosphate (PRPP) synthetase, which leads to an increased concentration of PRPP
- PRPP is a key determinant of purine synthesis and uric acid production
- The second is a deficiency of hypoxanthine-guanine phosphoribosyltransferase (HGPRT)
- HGPRT is responsible for the conversion of guanine to guanylic acid and hypoxanthine to inosinic acid
- These two conversions require PRPP as the cosubstrate and are important reactions involved in the synthesis of nucleic acids
- A deficiency in the HGPRT enzyme leads to increased metabolism of guanine and hypoxanthine to uric acid and to more PRPP to interact with glutamine in the first step of the purine pathway
- Complete absence of HGPRT results in the childhood Lesch-Nyhan syndrome, characterized by choreoathetosis, spasticity, mental retardation, and markedly excessive production of uric acid
- A partial deficiency of the enzyme may be responsible for marked hyperuricemia in otherwise normal, healthy individuals

UNDEREXCRETION OF URIC ACID

- Normally, uric acid does not accumulate as long as production is balanced with elimination
- About two thirds of the daily uric acid production is excreted in the urine and the remainder is eliminated through the gastrointestinal tract after enzymatic degradation by colonic bacteria
- The vast majority of patients (80% to 90%) with gout have a relative decrease in the renal excretion of uric acid for an unknown reason (primary idiopathic hyperuricemia)

- A decline in the urinary excretion of uric acid to a level below the rate of production leads to hyperuricemia and an increased miscible pool of sodium urate
- Almost all the urate in plasma is freely filtered across the glomerulus
- The concentration of uric acid appearing in the urine is determined by multiple renal tubular transport processes in addition to the filtered load.
- Evidence favors a four-component model including glomerular filtration, tubular reabsorption, tubular secretion, and postsecretory reabsorption
- Approximately 90% of filtered uric acid is reabsorbed in the proximal tubule, probably by both active and passive transport mechanisms
- There is a close linkage between proximal tubular sodium reabsorption and uric acid reabsorption
- A conditions that enhance sodium reabsorption (e.g., dehydration) also lead to increased uric acid reabsorption
- The exact site of tubular secretion of uric acid has not been determined; this too appears to involve an active transport process.
- Postsecretory reabsorption occurs somewhere distal to the secretory site.
- By enhancing renal urate reabsorption, insulin resistance is also associated with gout.
- The pathophysiologic approach to the evaluation of hyperuricemia requires determining whether the patient is overproducing or underexcreting uric acid
- This can be accomplished by placing the patient on a purine-free diet for 3 to 5 days and then measuring the amount of uric acid excreted in the urine in 24 hours
- As it is very difficult to maintain a purine-free diet for several days, this test is done infrequently in clinical practice
- Nevertheless, when it is performed, individuals who excrete more than 600 mg on a purine-free diet may be considered overproducers
- Nevertheless, when it is performed, individuals who excrete more than 600 mg on a purine-free diet may be considered overproducers

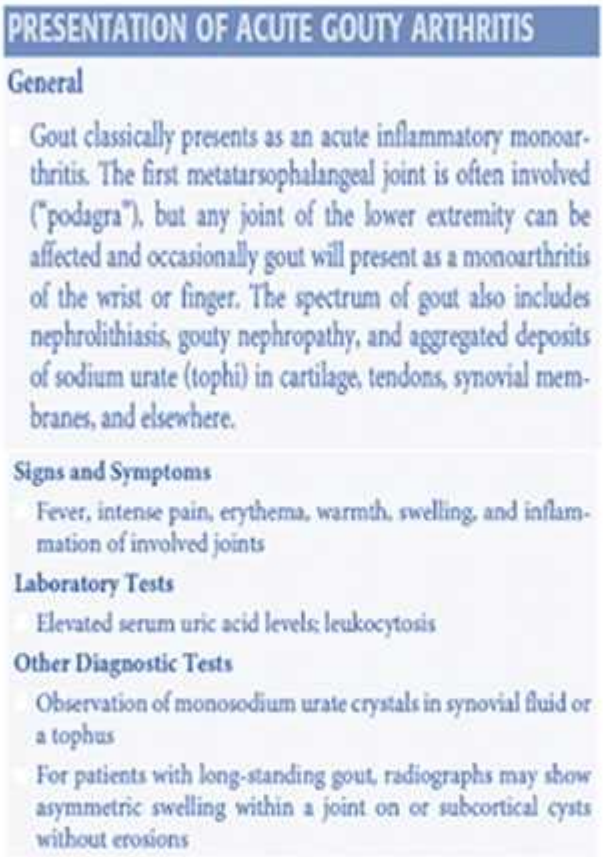
SUMMARY

- Prevalence is greater in men (5.9%; 6.1 million) than women (2.0%; 2.2 million)
- Caused by the deposition of monosodium urate crystals in tissues

- Uric acid is a metabolic by-product of purine catabolism

Gout

- Gout is diagnosed clinically by symptoms rather than laboratory tests of uric acid.
- In fact, asymptomatic hyperuricemia discovered incidentally generally requires no therapy because many individuals with hyperuricemia will never experience an attack of gout.
- These patients should still be encouraged to implement lifestyle measures to reduce serum urate concentrations.



PRESENTATION OF ACUTE GOUTY ARTHRITIS

General

Gout classically presents as an acute inflammatory monoarthritis. The first metatarsophalangeal joint is often involved ("podagra"), but any joint of the lower extremity can be affected and occasionally gout will present as a monoarthritis of the wrist or finger. The spectrum of gout also includes nephrolithiasis, gouty nephropathy, and aggregated deposits of sodium urate (tophi) in cartilage, tendons, synovial membranes, and elsewhere.

Signs and Symptoms

Fever, intense pain, erythema, warmth, swelling, and inflammation of involved joints

Laboratory Tests

Elevated serum uric acid levels; leukocytosis

Other Diagnostic Tests

Observation of monosodium urate crystals in synovial fluid or a tophus

For patients with long-standing gout, radiographs may show asymmetric swelling within a joint on or subcortical cysts without erosions

Clinical Presentation

ACUTE GOUTY ARTHRITIS

- A classic acute attack of gouty arthritis is characterized by rapid and localized onset of excruciating pain, swelling, and inflammation.
- The attack is typically monarticular at first, most often affecting the first metatarsophalangeal joint (great toe) and then, in order of frequency, the insteps, ankles, heels, knees, wrists, fingers, and elbows.

- In one half of initial attacks, the first metatarsophalangeal joint is affected, a condition commonly referred to as *podagra.*

Clinical Manifestations of Gout

Classic acute gout ("podagra")	Monoarticular arthritis Frequently attacks the first metatarsophalangeal joint, although other joints of the lower extremities are also frequently involved. Affected joint is swollen, erythematous, and tender.
Interval gout	Asymptomatic period between attacks.
Tophaceous gout	Deposits of monosodium urate crystals in soft tissues. Complications include soft tissue damage, deformity, joint destruction, and nerve compression syndromes such as carpal tunnel syndrome.
Atypical gout	Polyarthritis affecting any joint, upper or lower extremity. May be confused with rheumatoid arthritis or osteoarthritis.
Renal effects	Nephrolithiasis Acute and chronic gouty nephropathy

- Up to 90% of patients with gout will experience podagra at some point in the course of their disease.

- Atypical presentations of gout also occur. For elderly patients, gout can present as a chronic polyarticular arthritis that can be confused with rheumatoid arthritis or osteoarthritis.

- Additionally, theonset of gout may be less dramatic than the typical acute attack and have fewer clinical findings.

- Multiple small joints in the hands may be involved, especially in elderly women.

- The predilection of acute gout for peripheral joints of the lower extremity is probably related to the low temperature of these joints combined with high intraarticular urate concentration.

- Synovial effusions are likely to occur transiently in weight-bearing joints during the course of a day with routine activity.

- At night, water is reabsorbed from the joint space, leaving behind a supersaturated solution of monosodium urate, which can precipitate attacks of acute arthritis.

- Attacks generally begin at night with the patient awakened from sleep by excruciating pain.

- The development of crystal-induced inflammation involves a number of chemical mediators causing vasodilation, increased vascular permeability, complement activation, and chemotactic activity for polymorphonuclear leukocytes.

- Phagocytosis of urate crystals by the leukocytes results in rapid lysis of cells and a discharge of lysosomal and proteolytic enzymes into the cytoplasm.
- The ensuing inflammatory reaction is associated with intense joint pain, erythema, warmth, and swelling. Fever is common, as is leukocytosis.
- Untreated attacks may last from 3 to 14 days before spontaneous recovery.
- Although acute attacks of gouty arthritis may occur without apparent provocation, a number of conditions may precipitate an attack.
- These include stress, trauma, alcohol ingestion, infection,surgery, rapid lowering of serum uric acid by ingestion of uric acid-lowering agents.
- Other crystal-induced arthropathies that may resemble gout on Clinical Presentationare caused by calcium pyrophosphate dihydrate crystals(pseudogout) and calcium hydroxyapatite crystals, which are associated with calcific periarthritis, tendinitis, and arthritis.
- Acute flares of gouty arthritis may occur infrequently, but over time the interval between attacks may shorten if appropriate measures to correct hyperuricemia are not undertaken.
- Later in the disease, tophaceous deposits of monosodium urate crystals in the skin or subcutaneous tissues may be found.
- These tophi can be anywhere but are often found on the hands, wrists, elbows, or knees.
- It is estimated to take 10 or more years for tophi to develop.

Diagnostic Evaluation of Gout

- A definitive diagnosis of gout requires aspiration of synovial fluid from the affected joint and identification of intracellular crystals of monosodium urate monohydrate in synovial fluid leukocytes.
- Identification of monosodium urate crystals is highly dependent on the experience of the observer.
- Crystals are needle shaped, and when examined under polarizing light microscopy, they are strongly negatively birefringent.
- Crystals can be observed in synovial fluid during asymptomatic periods.
- If an affected joint is tapped, the resulting synovial fluid may have white cells and appear purulent. Such findings should always raise the question of infection.

- If any clinical features of infection are present, such as high fever, elevated white blood cell count, multiple joints affected, or an identified source of infection, proper diagnosis and treatment are critical.
- Patients with gout can have septic arthritis. Diabetes, alcohol abuse, and advanced age increase the likelihood of septic arthritis.
- In lieu of obtaining a synovial fluid sample from an affected joint to inspect for urate crystals, the clinical triad of inflammatory monoarthritis, elevated serum uric acid level, and response to colchicine can be used to diagnose gout.
- This approach has limitations, including a failure to recognize atypical gout presentations and the fact that serum uric acid levels can be normal or even low during an acute gout attack.
- In addition, use of colchicine as a diagnostic tool for gout is limited by lack of sensitivity and specificity for the disease.
- Other conditions such as psoriatic arthritis, sarcoidosis, and Mediterranean fever can respond to colchicine therapy.
- For patients with long-standing gout, radiographs may show punched-out marginal erosions and secondary osteoarthritic changes; however, in an acute first attack radiographs will be unremarkable.
- The presence of chondrocalcinosis on radiographs may indicate pseudogout.
- Some studies have recently examined the use of magnetic resonance imaging and computed tomography to obtain images for patients with gout; however, this is not currently considered part of normal practice.

URIC ACID NEPHROLITHIASIS

- Clinicians should be suspicious of hyperuricemic states for patients who present with kidney stones, as nephrolithiasis occurs in 10% to 25% of patients with gout.
- The frequency of urolithiasis depends on serum uric acid concentrations, acidity of the urine, and urinary uric acid concentration.
- Typically, patients with uric acid nephrolithiasis have a urinary pH of less than 6.0.
- Uric acid has a negative logarithm of the acid ionization constant of 5.5.
- Therefore, when the urine is acidic, uric acid exists primarily in the unionized, less soluble form.
- At a urine pH of 5.0, urine is saturated at a uric acid level of 15 mg/ dL (0.89 mmol/L).

- When the urine pH is 7.0, the solubility of uric acid in urine is increased to 200 mg/dL (11.9 mmol/L).
- For patients with uric acid nephrolithiasis, urinary pH typically is less than 6.0 and frequently less than 5.5.
- When acidic urine is saturated with uric acid, spontaneous precipitation of stones may occur.
- Other factors that predispose individuals to uric acid nephrolithiasis include excessive urinary excretion of uric acid and highly concentrated urine.
- The risk of renal calculi approaches 50% in individuals whose renal excretion of uric acid exceeds 1,100 mg/ day (6.5 mmol/day).
- In addition to pure uric acid stones, hyperuricosuric individuals are at increased risk for mixed uric acid–calcium oxalate stones and pure calcium oxalate stones.
- Uric acid stones are usually small, round, and radiolucent.
- Uric acid stones containing calcium are radiopaque.

GOUTY NEPHROPATHY

- There are two types of gouty nephropathy: acute uric acid nephropathy and chronic urate nephropathy.
- In acute uric acid nephropathy, acute renal failure occurs as a result of blockage of urine flow secondary to massive precipitation of uric acid crystals in the collecting ducts and ureters.
- This syndrome is a well-recognized complication for patients with myeloproliferative or lymphoproliferative disorders and is a result of massive malignant cell turnover, particularly after initiation of chemotherapy.
- Chronic urate nephropathy is caused by the long-term deposition of urate crystals in the renal parenchyma.
- Microtophi may form, with a surrounding giant-cell inflammatory reaction.
- A decrease in the kidneys' ability to concentrate urine and the presence of proteinuria may be the earliest pathophysiologic disturbances.
- Hypertension and nephrosclerosis are common associated findings.
- Although renal failure occurs in a higher percentage of gouty patients than expected, it is not clear if hyperuricemia per se has a harmful effect on the kidneys.
- The chronic renal impairment seen in individuals with gout may result largely from the coexistence of hypertension, diabetes mellitus, and atherosclerosis.

TOPHACEOUS GOUT

- Tophi (urate deposits) are uncommon in the general population of gouty subjects and are a late complication of hyperuricemia.
- The most common sites of tophaceous deposits for patients with recurrent acute gouty arthritis are the base of the great toe, helix of the ear, olecranon bursae, Achilles tendon, knees, wrists, and hands
- Eventually, even the hips, shoulders, and spine may be affected.
- In addition to causing obvious deformities, tophi may damage surrounding soft tissue, cause joint destruction and pain, and even lead to nerve compression syndromes including carpal tunnel syndrome.

Summary

- Gout is different from hyperuricemia

ACUTE GOUTY ARTHRITIS

- A classic acute attack of gouty arthritis is characterized by rapid and localized onset of excruciating pain, swelling, and inflammation

URIC ACID NEPHROLITHIASIS

The frequency of urolithiasis depends on serum uric acid concentrations, acidity of the urine, and urinary uric acid concentration

TOPHACEOUS GOUT

- Tophi (urate deposits) are uncommon in the general population of gouty subjects and are a late complication of hyperuricemia

CANCER

General biology of cancer

Neoplasm/ Tumour - *"A mass of tissue formed as a result of abnormal**, excessive, uncoordinated, autonomous and purposeless proliferation of cells**"*

- **Oncology –** Branch of science dealing with the study of neoplasm
- Transformation from a living normal cell into a living tumor cell

Basic features of change in neoplasia

- Change is irreversible; becomes fixed character of a transformed cell

- Acquired fixed character is heritable; tumor cell divide to give tumor cell
- Change once occurred is self-perpetuating
- Tumor cell has uncontrolled passion for continued proliferation

Classification of tumors

- Based on the nature of tumors, they are classified as

  Benign tumor – Harmless and self-limited

  Malignant tumor – Harmful and rapidly growing

- Names of every tumor ends with **'oma'**
- Malignant tumor of epithelial tissue – **Carcinoma**
- Malignant tumor of connective tissue - **Sarcoma**

Classification of tumor based on tissue of origin

Tissue of origin	**Benign**	**Malignant**
Epithelial tumors		
1. Squamous epithelium	Squamous cell papilloma	Squamous cell carcinoma
2. Transitional epithelium	Transitional epithelium papilloma	Transitional epithelium carcinoma
3. Glandular epithelium	Adenoma	Adenocarcinoma
4. Hepatocytes	Liver cell adenoma	Hepatocellular carcinoma (Hepatoma)

Tissue of origin (Non epithelial tumors)	**Benign**	**Malignant**
Adipose tissue	Lipoma	Liposarcoma
Fibrous tissue	Fibroma	Fibrosarcoma
Cartilage	Chondroma	Chondrosarcoma
Bone	Osteoma	Osteosarcoma

Blood vessels	Haemangioma	Angiosarcoma
Nerve cells	Ganglia Neuroma	Neuroblastoma

Contrasting features of benign and malignant tumor

Features	Benign	Malignant
Macroscopic features		
1. Boundaries	Encapsulated/ well circumscribed	Irregular & poorly circumscribed
2. Surrounding tissues	Often compressed	Usually invaded
3. Size	Usually small	Often large
4. Secondary changes	Occurs less often	Occurs more often
Microscopic Features		
1. Pattern	Closely resembles the tissue of origin	Poor resemblance to the tissue of origin
2. Basal polarity	Retained	Lost
3. Pleomorphism	Normal	Increased
Features	Benign	Malignant
Microscopic features (cont..d)		
4. Neuclio- cytoplasmic ratio	Normal	Increased
5. Hyperchromatism	Absent	Present
6. Mitosis	Always typical mitosis	Atypical & abnormal mitosis
7. Tumor giant cells	May be present but with atypical nucleus	Always present with atypical nucleus
8. Cytoplasm	With normal constituents	Elements are reduced or lost
9. Functions	Usually well maintained	Retained/ lost/ abnormal
Growth rate	Usually slow	Rapid
Local invasion	Often compresses the surroundings; no invasion/ infiltration	Invade & infiltrate the adjacent tissue
Metastatis (Spreading)	Absent	Present

Structure of tumor

Tumor mass consists of:

a. Parenchyma
b. Stroma

Parenchyma

- Formed by proliferating tumor cells
- Parenchyma of benign tumor – organised pattern with resemblance to tissue of origin, **differentiation**
- Parenchyma of malignant tumor – unorganised, atypical, distorted, relation of tumor cell with basement is lost, **anaplasia**

Stroma

- Supporting tissue of tumor
- Consists of fibrous tissue carrying blood vessels for nourishing tumor cell
- More malignant the tumor, Cirrhous
- Carcinoma with scanty stroma – celluloid & medullary
- New blood vessels form from pre existing onesless is the fibrous tissue
- Carcinoma with extensive stroma – with the help of a factor, "tumor angiogenesis factor"

Spread of cancer

(Two mechanism for the spread of cancer)

Direct spread (Invasion, Infilteration, direct spread)	Metastasis
• Spread to surrounding tissue; no loss of contunity between primary tumor & secondary extension masses • Benign tumors push aside the surrounding normal tissues without invading or metastasing • Maliganant tumor infiltrates, invades & destroys surrounding tissues	• Transplantation of tumor cells from the primary mass to distant cell without an anatomic continuity between primary and secondary masses • Important feature to distinguish malignant from a benign tumor

Routes of spread of cancer

1. Infiltration of tissue spaces

- Tissue spaces - preformed passages; paths of least resistance
- Most vulnerable tissues – soft tissues – adipose, muscle,
- Gamete/ compact tissues like capsule of organs, cartilage and bone (not marrow) offer greater resistance
- Tissue subjected to infiltration are destroyed by the proteolytic enzymes & lytic substances elaborated by cancer tissue
- Tissue space invasion brings the tumor cell in direct contact with normal cells, lymphatic and blood vessels

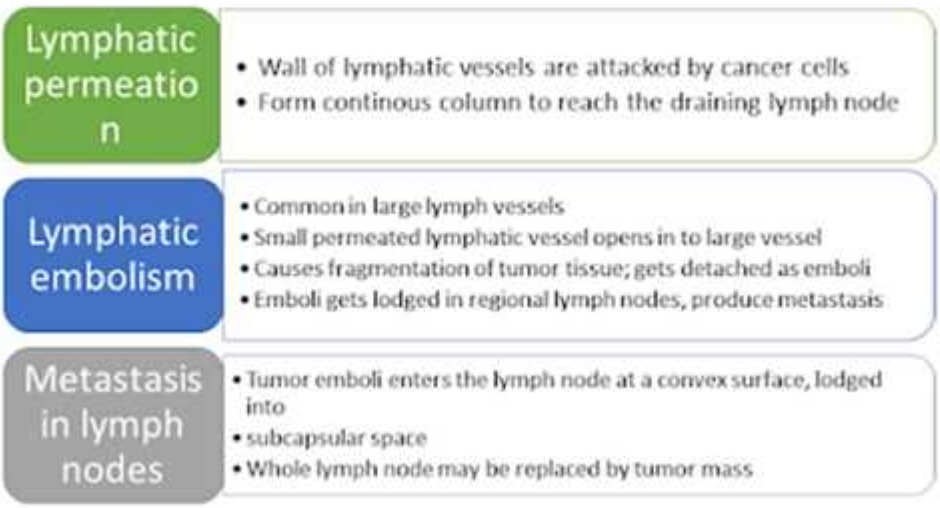
2. Hematogenous spread:

- Carcinoma of lungs, thyroid, kidney and the prostate spread through blood vessels

Tumor cells enter blood stream by 2 ways

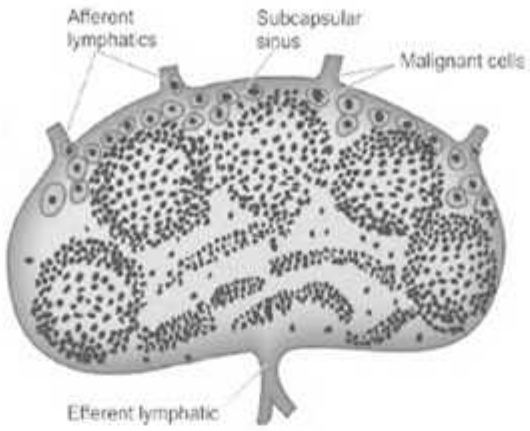
a. Via thorasic duct – either by perforation of vein or by lymphatic drainage
b. By direct invasion of blood vessels (large veins, venules & capillaries); arteries not involved due to their thick wall

3. Spread via lymphatics: Most common with carcinoma; results in both invasion & metastasis

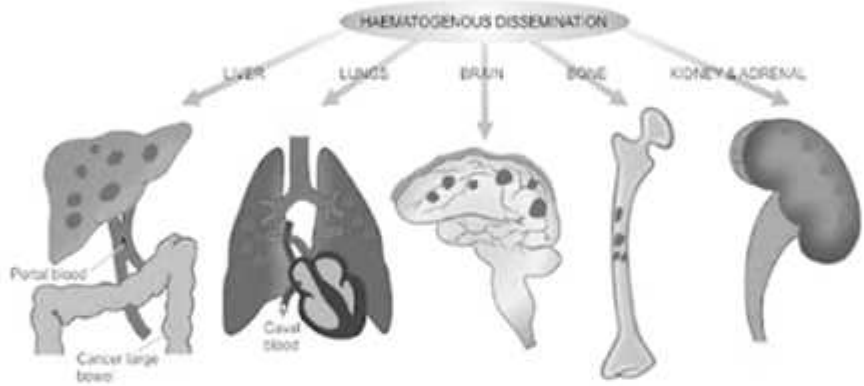


Spread via lymphatics

Lymphatic spread begins by lodgement of tumour cells in subcapsular sinus via afferent lymphatics entering at the convex surface of the lymph node



Hematogenous spread



4. Spread via serous sacs

- Spread through peritoneal cavity; common in cancer of GIT & ovary
- Trans pleural spread - in carcinoma of lungs and breast
- Trans pericardial spread may also occur

5. Spread along epithelium line surfaces

- Intact epithelium, mucous coat acquires resistance for penetration of tumor
- Implantation tumor – tumor spread along the surface of epithelium

6. Spread via CSF

- Cerebrospinal cavities are affected by the escape of tumor cells from
- the malignant tumor in the brain or meninges

Summary

- A tumour is a mass of tissue formed as a result of abnormal, excessive, uncoordinated, autonomous and purposeless proliferation of cells
- Tumors are classified as benign and malignant
- Benign tumors are harmless and do not spread while malignant tumors are harmful and spread
- Tumor is made up of parenchyma and stroma
- Tumor spread by two mechanism – Haematogenous spread and lymphatic spread

Evidence of malignancy

A. Clinical evidence

- Age of patient – cancer, a disease of adults
- Rate of growth – rapid growth of tumor indicates malignancy
- Evidence of infiltration - sign of malignancy
- Presence of metastasis – distant metastasis indicates cancer that is not operable

B. Macroscopic evidence

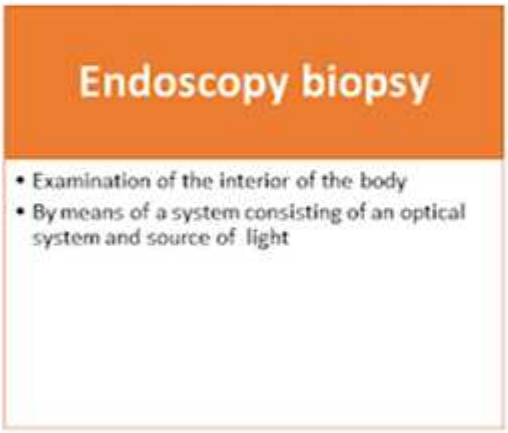
- Tumor makes its appearance either as a mass or as an ulcer
- Size & shape of different tumor are different
- **Benign tumor** – Sharply marked from surrounding tissues, shows fibrous capsule all around
- **Malignant tumor** – poorly defied, capsule is missing
- Different tumor may have different color
- Malignant melanoma – **jet black**
- Renal cell carcinoma – **yellow**
- Most of the cancers are greyish white in color

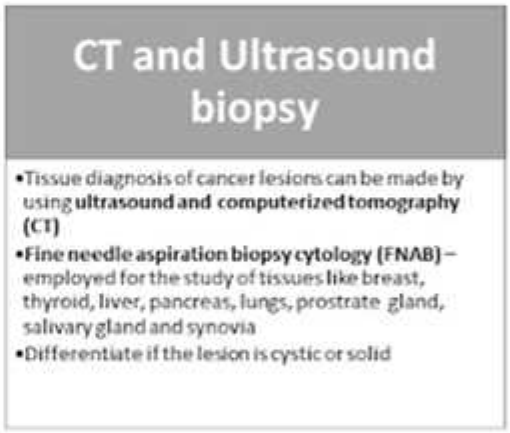
C. Microscopic evidence

- **Cytological diagnosis :**
  - Discharges, secretion, excretion and effusion in body cavities examined for the presence of cancer cells

- Thin smear of the materials are fixed, wet with ethyl alcohol and stained by special techniques

- **Aspiration biopsy**
  - Tumor mass is aspirated with a needle or syringe
  - Cylinder portion of tumor tissue is obtained
  - Histological sections are prepared
  - If fluid obtained – Smears are made for cytological diagnosis
- **Incisional biopsy**
  - Portion of tumor tissue removed surgically, examined histologically
- **Excisional biopsy**
  - Whole of small lesion excised along with a safe margin of healthy tissue





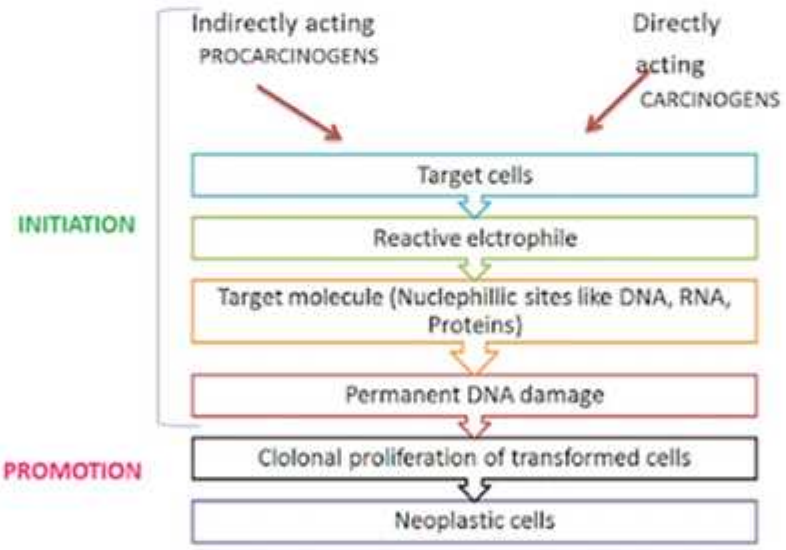
Tumor Marker

- Biochemical assays of products elaborated by the tumour cells in blood or other body fluids
- Tumour markers include: cell surface antigens (or oncofoetal antigens), cytoplasmic proteins, enzymes, hormones and cancer antigens

Tumor markers

Marker	Cancer
1. ONCOFOETAL ANTIGENS:	
i. *Alpha-foetoprotein (AFP)*	Hepatocellular carcinoma, non-seminomatous germ cell tumours of testis
ii. *Carcinoembryonic antigen (CEA)*	Cancer of bowel, pancreas, breast
2. ENZYMES:	
i. *Prostate acid phosphatase (PAP)*	Prostatic carcinoma
ii. *Neuron-specific enolase (NSE)*	Neuroblastoma, oat cell carcinoma lung
iii. Lactic dehydrogenase (LDH)	Lymphoma, Ewing's sarcoma
3. HORMONES:	
i. *Human chorionic gonadotropin (hCG)*	Trophoblastic tumours, non-seminomatous germ cell tumours of testis
ii. *Calcitonin*	Medullary carcinoma thyroid
iii. *Catecholamines and vanillylmandelic acid (VMA)*	Neuroblastoma, pheochromocytoma
iv. *Ectopic hormone production*	Paraneoplastic syndromes
4. CANCER ASSOCIATED PROTEINS:	
i. *CA-125*	Ovary
ii. *CA 15-3*	Breast
iii. *CA 19-9*	Colon, pancreas, breast
iv. *CD30*	Hodgkin's disease, anaplastic large cell lymphoma (ALCL)
v. *CD25*	Hairy cell leukaemia (HCL), adult T cell leukaemia lymphoma (ATLL)
vi. *Monoclonal immunoglobulins*	Multiple myeloma, other gammopathies
vii. *Prostate specific antigen (PSA)*	Prostate carcinoma

Etio-pathogenesis of cancer



CARCINOGENS

Carcinogens are categorized into 4 groups

- Chemical carcinogens – includes chemicals and drugs
- Physical carcinogens – includes radiations
- Hormonal carcinogens
- Biological carcinogens – Viruses

Chemical carcinogenesis

Process of cellular transformation of chemical carcinogen occurs in

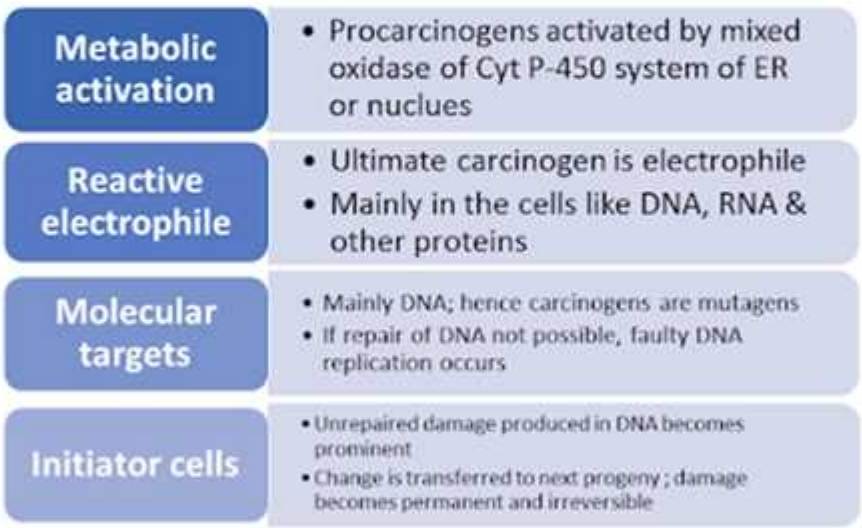
2 stages - Initiation of carcinogenesis

- Promotion of carcinogenesis

 Initiation of carcinogenesis

2 types of chemical carcinogens – **directly acting & indirectly acting**

- **Directly acting** (alkylating agents) - Does not require conversion to become carcinogenic; Can induce cellular transformation
- **Indirectly acting/ Procarcinogens** (aromatic amines, azodyes)– require metabolic conversion to become active



Promotion of carcinogenesis

- In this stage, cells are selectively stimulated to proliferate by activation of growth factor
- Promoters of carcinogens – Phenols, Hormones, artificial sweeteners, drugs like phenobarbitone
- **Pro carcinogenesis** - when 2 carcinogens acting simultaneously to enhance the effect

Physical carcinogenesis

Radiation carcinogenesis

- Ionising radiations & UV rays can cause cancer
- UV rays – immune suppression &DNA damage

Eg. Squamous cell carcinoma, basal cell carcinoma, malignant melanoma

- Ionising radiations – X- rays, α- rays, β- rays, radioactive isotope, protons, neutrons

Eg. Blood cancer, cancer of thyroid, skin, lungs, breast & salivary glands

Non radiation carcinogens

- Mechanical injury as a result of gall bladder stones, kidney stones, scars of bones & trauma
- Other examples include glass and plastics

Hormonal carcinogenesis

Organs or tissues which undergo proliferation under the influence of hormones are likely to develop cancer

Examples:

- **Estrogen induced cancer** – breast cancer, squamous cell carcinoma, carcinoma of cervix, tumor of myometrium
- **Contraceptive steroids** – oral contraceptives for long time can cause breast and liver cancer
- **Anabolic steroids** – increases risk of developing cancer

Biological carcinogenesis

- Viruses cause different type of cancer (oncogenic viruses)
- Parasites cause cancer of urinary bladder
- Bacteria – gastric lymphoma and carcinoma

Examples of viruses causing cancer

- Human papilloma virus
- Epstein barr virus
- Hepatitis B virus

Pathogenesis of cancer

- Basis for tumor formation – change in genetic factors leading to non-lethal damage to cells
- 2 genes involved during the development of cancer

- Growth promoter proto oncogene
- Growth supressor anti oncogene

- Most well studied tumor suppressor gene – P_{53} gene
- P_{53}, critical gate keeper, prevent formation of cancer
- Localized in nucleus, transcribe several gene when required

When DNA damage by irradiation, mutagenic chemical – increase in

P_{53} gene – it binds to DNA – simulates its repair

2 major effects of P_{53} gene

- Cell cycle arrest
- Apoptosis

- Cell cycle arrest in late G1 phase – prevent cell from entering into next cell cycle
- Allows time for DNA repair
- **If damaged repaired** – stimulates MDM2 gene, down regulates P_{53} gene , relieve cell block
- **If damaged not repaired** – cell apoptosis
- Inhibition of P_{53} gene by its mutation may leads to cancer

Summary

- Malignancy can be determined by evidences obtained by clinical, microscopical examination of tumor
- Carcinogens are the agents that causes cancer
- Cancinogens can be physical, chemical, hormonal or biological
- Basis for tumor formation is change in genetic factors leading to non-lethal damage to cells
- 2 genes involved during the development of cancer growth promoter proto oncogene and growth suppressor anti oncogene
- P_{53} gene is mainly involved in the development of cancer

Tuberculosis

- Chronic granulomatous disease caused by *Mycobacterium tuberculosis*
- Usually affects lungs
- Organism is a strict aerobe and thrives best in tissues with high oxygen tension such as in the apex of the lung

Risk factors

- Person's whose immune system is weakened (HIV infected people)
- Alcohol or drug abuse
- Diabetic persons
- Regular contact with TB infected persons
- Multidrug resistance TB occurs if Patients do not complete the course of antibiotic therapy

Symptoms of Tuberculosis

- Persistent cough for 15 days
- Fever, Chest pain, haemoptysis, dyspnoea, night sweats, tiredness, loss of apetite, rapid weight loss, swollen glands, signs of pneumonia
- Joint pain
- TB of GIT - abdominal pain
- TB in brain - altered mental status, headache, confusion and coma
- Weakness due to anemia, backpain, paralysis

Mode of transmission of Tuberculosis

- **Inhalation** of organisms present in fresh cough droplets or in dried sputum from an open case of pulmonary tuberculosis
- **Ingestion of the organisms**
- Development of tonsillar or intestinal tuberculosis
- Mode of infection of human tubercle bacilli
- Ingestion of bovine tubercle bacilli from milk of diseased cows

- **Inoculation** of the organisms into the skin
- **Transplacental route**
- Development of congenital tuberculosis in foetus from infected mother
- Rare mode of transmission

Spread of tuberculosis

- **Local spread**: macrophages carrying the bacilli into the surrounding tissues
- **Lymphatic spread**:
- Infection of lymphoid tissues
- Bacilli pass into lymphoid follicles of pharynx, bronchi, intestines or regional lymph nodes
- Regional tuberculous lymphadenitis
- **Haematogenous spread**
- Result of tuberculous bacillaemia
- Drainage of lymphatics into the venous system or due to caseous material
- Escaping through ulcerated wall of a vein
- Millet seed-sized lesions in lungs, liver, kidneys, bones and other tissues
- Known as miliary tuberculosis.

Primary disease

- An initial infection with bacilli
- In areas of high TB prevalence – this form of disease is often seen in children
- Frequently localized to the middle and lower lobes of the lungs
- Lesions – calcified nodule (Ghon lesion)

Secondary TB

- Adult type, reactivation, or secondary TB - endogenous reactivation of latent infection
- Localized to the apical and posterior segments of the upper lobes

- Oxygen consumption favors mycobacterial growth
- Extent of lung parenchymal involvement varies greatly, from small infiltrates to extensive cavitary disease

Summary

- Tuberculosis is an granulomatous and infectious disorder that will typically occur in the lung called pulmonary tuberculosis and if it occurs for other organs it's called extra pulmonary tuberculosis
- Tubercle bacillus or Koch's bacillus or Mycobacterium tuberculosis causes tuberculosis in the lungs and other tissues of human body by hematogenous, lympahtic or transplacental route

Urinary tract infections (UTIs)

- A wide variety of syndromes
- Including urethitis, cystitis, prostatitis, and pyelonephritis
- Presence of microorganisms in the urinary tract that cannot be accounted for by contamination
- Infection may be limited to the growth of bacteria in the urine
- Frequently may not produce symptoms

Classification of UTI

Lower tract infection

- Cystitis
- Urethritis
- Prostatitis

Upper tract infection

- Pyelonephritis involving the kidneys

According to Degree

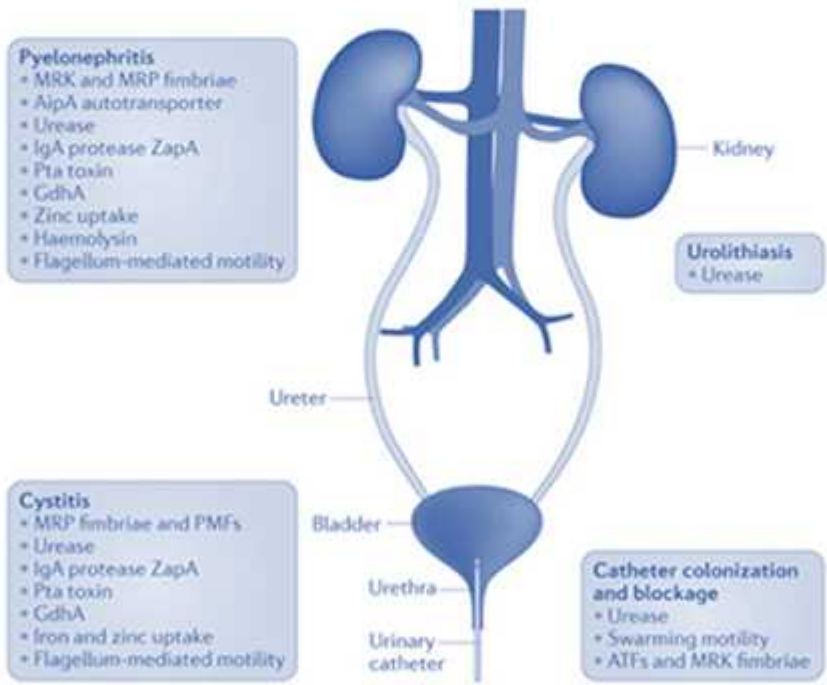
Complicated

- Predisposing lesion of the UT
- Congenital abnormality or distortion of the UT

- A stone a catheter
- Prostatic hypertrophy, obstruction, or neurological deficit
- All can interfere with the normal flow of urine and urinary tract defenses.

Recurrent UTIs

- Multiple symptomatic infections with asymptomatic periods
- ***Re infection***
  - Caused by a different organism than originally isolated and account for the majority of recurrent UTIs
- *Relapse*
  - Repeated infections with the same initial organism and usually indicate a persistent infectious source



Etiology of UTI

The microorganism that cause UTIs usually originate from the bowel flora of the host

Uncomplicated UTI:

- *E. coli* accounts for 85%
- *S. saprophyticus* 5-15%

- *K. pneumoniae*, Pseudomonas, and Enterococcus 5-10%
- *S. epidermidis* if isolated should be considered a contamination

Complicated UTIs

- Occurs because of anatomic, functional, or pharmacological factors
- Predisposes the patient to persistent infection, recurrent infection, or treatment failure

Clinical presentations

Lower tract infection

- Include dysuria, urgency, frequency, nocturia, suprapubic heaviness, and hematuria in women
- No systemic symptoms

Upper tract infection

- Flank pain, costovertebral tenderness, abdominal pain, fever, nausea, vomiting and malaise.

Elderly patients

- Frequently do experience specific urinary symptoms
- Altered mental status, change sin eating habits, or GI symptoms

Patients with catheters

- Will have no lower tract symptoms
- Just flank pain and fever

Pathophysiology of UTI

- Infection spreads from renal pelvis to renal cortex
- Kidney grossly edematous; localized abscesses in cortex surface
- *E. Coli* responsible organism for 85% of acute pyelonephritis; also Proteus, Klebisella

Manifestations of UTI

- Rapid onset with chills and fever
- Malaise

- Vomiting
- Flank pain
- Costovertebral tenderness
- Urinary frequency, dysuria

Summary

- UTI is defined as the presence of microorganisms in the urinary tract
- Escherichia coli, which accounts for 85% of community-acquired infections and is a frequently isolated pathogen , but it accounts for less than 50% of infections
- Between the ages of 1 and 5 years, UTIs occur more frequently in females
- UTI can be acquired through three routes ascending, hematogenous and lymphatic
- Natural host defence mechanism including free flow of urine, low pH, high osmolality, high ammonia are bacteriostatic in nature and changes in these defence mechanism will lead to urinary tract infection

AIDS

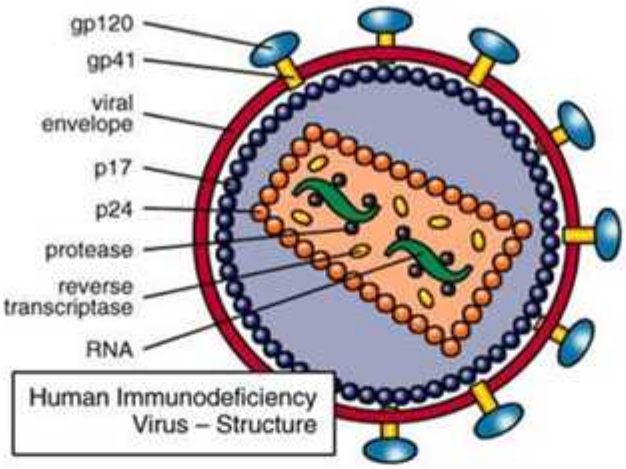
HIV

- HIV stands for the Human Immunodeficiency Virus
- A group of viruses known as retroviruses
- After getting into the body, the virus kills or damages cells of the body's immune system
- Body tries to keep up by making new cells or trying to contain the virus
- Destroys the body's ability to fight infections and certain cancers

TYPES OF HIV

- HIV 1 & HIV 2
- Although all HIV viruses are similar
- Small variations or mutations in the genetic material of the virus create drug-resistant viruses
- Larger variations in the viral genes are found in different viral subtypes
- HIV-1 is the predominant subtype that causes HIV/AIDS

HIV Structure



AIDS

- **Acquired Immunodeficiency Syndrome**
- HIV is the virus that causes AIDS
- Disease limits the body's ability to fight infection
- A person with AIDS has a very weak immune system
- No Cure

Etiology of HIV

- Virus can enter the body through the lining of the vagina, vulva, penis, rectum, or mouth – during sexual contact
- HIV frequently spreads among injection
- Drug users who share needles or syringes contaminated with blood from an infected person
- Women can transmit HIV to their babies during pregnancy or birth
- When infected maternal cells enter the baby's circulation, or through breastfeeding
- HIV can be spread in health-care settings through accidental needle sticks or contact with contaminated fluid
- Very rarely - transfusion of contaminated blood or blood components
- People who already have a sexually transmitted infections, such as
    - Syphilis, genital herpes

- Chlamydial infection
- Human papillomavirus (HPV)
- Gonorrhea or bacterial vaginosis

Pathogenesis of HIV

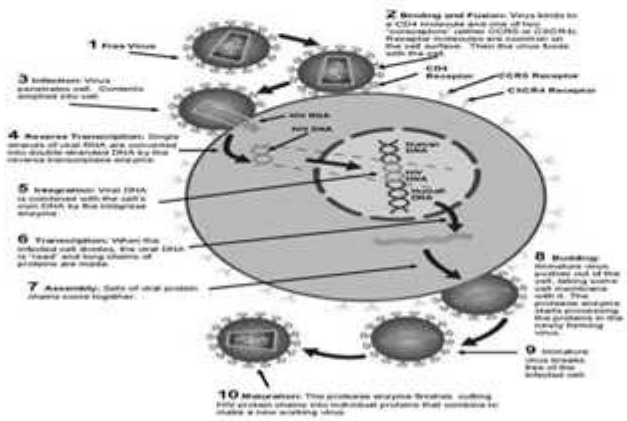
Two main systems which are targets of HIV

- Immune system
- CNS

Immunopathogenesis

- Profound immunosuppression
- Depletion of CD4+ T- cells
- Infections & impairment of function
- Macrophages and dendritic cells are main targets

Sequence of events



- Selective tropism and internalisation
- Uncoding and proviral DNA integration
- Budding and cynctia formation
- Cytopathic effect
- Effect on monocyte and macrophages
- B- cell dysfunction

- CNS involvement

Signs & symptoms of HIV

- Many people with HIV do not know they are infected
- No symptoms after infection with HIV
- Others - flu-like illness within several days to weeks after exposure
- Early HIV symptoms - fever, headache, tiredness, and enlarged lymph nodes in the neck

Major symptoms

- Weight loss
- Chronic diarrhoea for more than one month
- Fever lasting for more than one month

Minor

- Recurrent candidiasis in oropharyngeal membrane
- Lymph adenopathy
- Persistent cough for more than 1 month
- Pruritic dermatitis

- The infections that happen with AIDS are called opportunistic infections
  - Pneumonia caused by *Pneumocystis*
  - brain infection with toxoplasmosis which can cause trouble thinking or symptoms that mimic a stroke
  - widespread infection with a bacteria called MAC (mycobacterium avium complex) which can cause fever and weight loss
  - Certain fungi like histoplasmosis, which can cause fever, cough, anemia, and other problems
  - lymphoma in (a form of cancer of the lymphoid tissue) in the brain, which can cause fever and trouble thinking
  - A cancer of the soft tissues - Kaposi's sarcoma, which causes brown, reddish, or purple spots that develop on the skin or in the mouth

Summary

- HIV is a retro virus that causes AIDS and weekens the immune system of the body
- Main causes are IV drug users, multiple sex partners, sex with infected partner, in hospital needle sticks, contamination of blood products, pregnant mothers to babies
- Currently 40 million people live with that and 25 million died
- Free virus after binding and fusion in to the cell wall causes infection by reverse transcription followed by integration and transcription which forms mature virus

Polycystic Ovary Syndrome (PCOS)

Stein and Leventhal

First to recognize an association between the **presence of polycystic ovaries and signs of hirsutism amenorrhea** (oligomenorrhea, obesity)

Polycystic Ovarian Disease

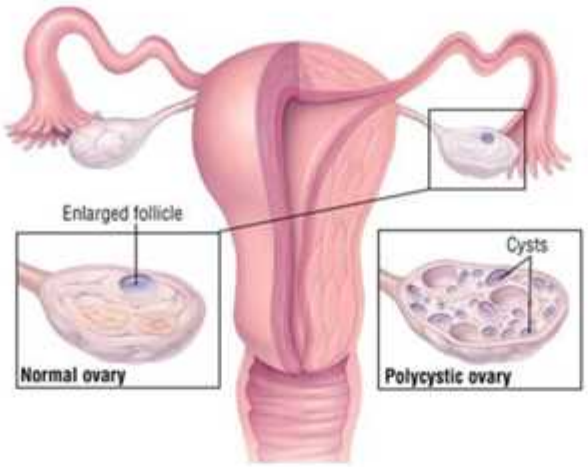
After successful wedge resection of the ovaries in women diagnosed with Stein-Leventhal syndrome, menstrual cycles become regular and the patients were able to conceive (polycystic ovarian disease)

Polycystic ovarian syndrome

Biochemical, clinical and endocrinological abnormalities have shown an array of underlying abnormalities; hence condition known as polycystic ovarian syndrome(PCOS)

Syndrome ”O”

- Ovarian confusion
- Ovulation disruption
- Over-nourishment
- Overproduction of insulin



Criteria of the PCO

- Presence of menstrual abnormalities and anovulation
- Presence of clinical and/or biochemical hyperandrogenaemia
- Ultrasound examination - peripheral cysts (10 or more) less than 10mm in size in an enlarged ovary with significant increase in the central stroma

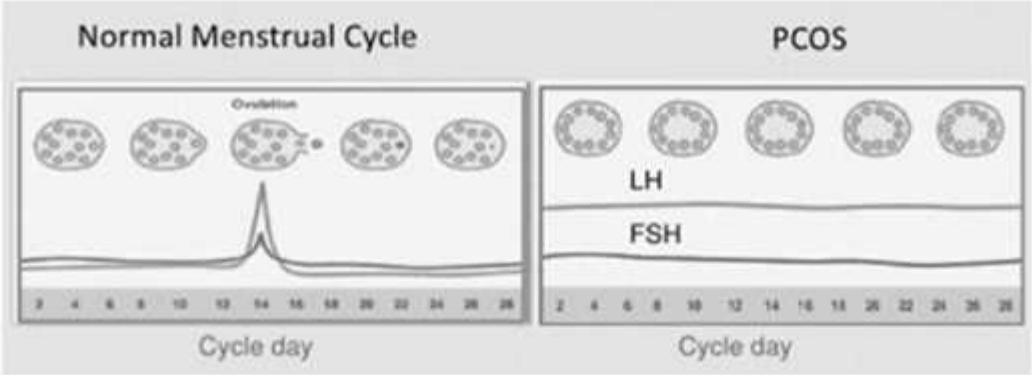
 Absence of hyperprolactinaemia or thyroid disease

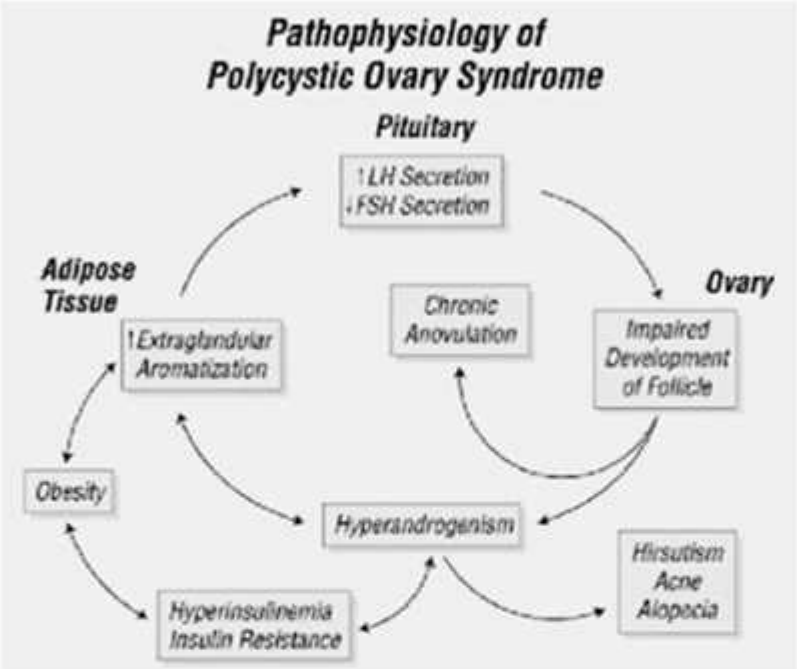
 Absence of late-onset congenital adrenal hyperplasia

 Absence of Cushing's syndrome

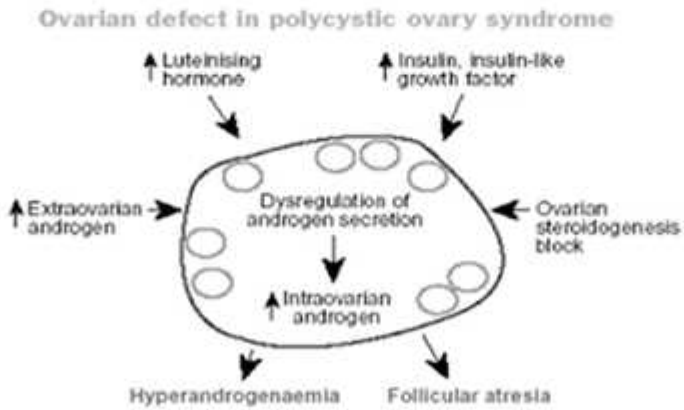
Etiology of PCOS

- Neuroendocrine derangement
  - ↑LH relative to FSH
- Hyperinsulinemia
  - Defect in insulin action or secretion
- Androgen excess
  - Ovarian and adrenal



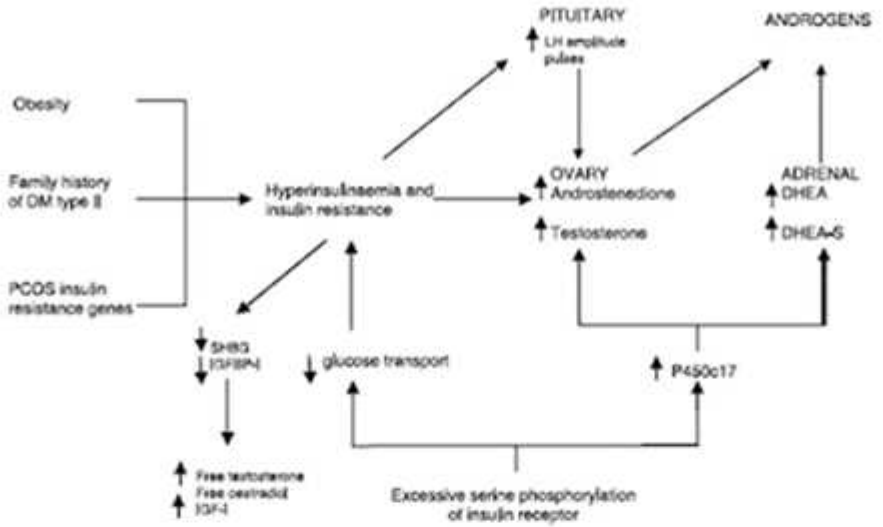


Functional Hyperandrogenism



The cardinal feature is functional ovarian hyperandrogenism.

Pathways leading to Androgen excess in PCOS



Clinical Features of PCOS

- Menstrual abnormalities, Infertility "anovulation", Hirsutism, acne, aloplecia, Increased risk of atherosclerosis & cardiovascular events
- Increased risk of diabetes mellitus in patients with hyperinsulinemia
- Increased risk of endomentreal cancer & Breast cancer
- Hyperlipidemia with its impact on atherosclerotic changes
- Hypertension observed later in life
- Obesity 40% with health risks including saphenous varicosities, hemorrhoids, hernias & osteoarthritis
- Several mental health problems, depression, anxiety

Summary

- Biochemical, clinical and endocrinological abnormalities have shown an array of underlying abnormalities; hence condition known as polycystic ovarian syndrome
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Functional Hyperandrogenism

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- Androgen excess - Ovarian and adrenal

Criteria of the PCO

- Presence of menstrual abnormalities and anovulation
- Presence of clinical and/or biochemical hyperandrogenaemia
- Ultrasound examination - peripheral cysts (10 or more) less than 10mm in size in an enlarged ovary with significant increase in the central stroma

 Absence of hyperprolactinaemia or thyroid disease

 Absence of late-onset congenital adrenal hyperplasia

 Absence of Cushing’s syndrome

Etiology of PCOS

- Neuroendocrine derangement
  - ↑LH relative to FSH
- Hyperinsulinemia
  - Defect in insulin action or secretion
- Androgen excess
  - Ovarian and adrenal

Functional Hyperandrogenism

Pathways leading to Androgen excess in PCOS

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Clinical Features of PCOS

- Menstrual abnormalities, Infertility “anovulation”, Hirsutism, acne, aloplecia, Increased risk of atherosclerosis & cardiovascular events
- Increased risk of diabetes mellitus in patients with hyperinsulinemia
- Increased risk of endomentreal cancer & Breast cancer
- Hyperlipidemia with its impact on atherosclerotic changes
- Hypertension observed later in life
- Obesity 40% with health risks including saphenous varicosities, hemorrhoids, hernias & osteoarthritis
- Several mental health problems, depression, anxiety

Summary

- Biochemical, clinical and endocrinological abnormalities have shown an array of underlying abnormalities; hence condition known as polycystic ovarian syndrome
- Menstrual abnormalities, Infertility “anovulation”, Hirsutism, acne, aloplecia, Increased risk of atherosclerosis & cardiovascular events
- Neuroendocrine derangement - ↑LH relative to FSH
- Hyperinsulinemia- Defect in insulin action or secretion
- Androgen excess - Ovarian and adrenal